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January-February, 1925

ORGANOTHERAPY, PRESENT ACHIEVEMENTS AND FUTURE PROSPECTS*

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INTRODUCTORY

Since the membership of this Academy is representative of all branches and specialties of clinical medicine, it has seemed judicious to select for this address a phase of endocrinology interesting to all practitioners. Although this youthful field of internal medicine may be regarded by some as rather narrow, arrogant and obstreperous, it does in truth reach out and touch closely each and all of the subdivisions of medical practice and preclinical investigation. A brief elaboration of this conception may not be inappropriate at this point.

Thus, the opthalmologist has occasion to notice exopthalmos and the other "eye signs" of thyroid disease; or be the first to suspect diabetes mellitus because of retinal abnormalities; he will be called upon to determine precisely the degree of bitemporal hemianopsia or diminution of vision in instances of pituitary tumor that impinge upon the optic chiasm. Indeed he has gone further and attempted to abort an early cataract with thyroid extract (with some success), and is giving serious con-

* Address delivered before the Portland Academy of Medicine, Portland, Oregon, Nov. 13, 1924. Lantern slides were used to illustrate the paper, which are not reproduced in this publication.

sideration to the incretory origin of glaucoma. The otorhinolaryngologist may recognize a myxedematous infiltration of the Eustachian tubes as the cause of a patient's deafness; he may notice the nasal deformity of acromegaly, the saddle nose of cretinism, the thick tongue of hypothyroidism. Some of his confreres have contributed some thoughtful speculations as to an endocrine responsibility for certain forms of asthma and vasomotor rhinitis. And it may be noted in this connection that the occasional sudden and considerable gain in weight following tonsillectomy in some children is not without endocrine significance.

The orthopedist will be consulted for myalgic and arthritic aches and pains, which may depend upon the excessive strain of an endocrine adiposity; or he may perceive that a progressive kyphosis and bulging sternum is merely a feature of an acromegalic hypophysis. The urologist will be consulted by anxious parents because their son's genitalia retain an infantile appearance; and they will be besieged by anxious husbands who fear lest they "lose their manhood" or who yearn for rejuvenation. The gynecologist does not lack for patients suffering from "hormonic imbalance"; indeed, it is essential that he be alert and alive to the fact that a "fallen womb" is not the invariable explanation of dysmenorrhoea; and that hypothyroidism may cause menorrhagia and hypopituitarism cause amenorrhoea, and that neither can be diagnosed through a speculum. He should be aware of the fact that some cases of sterility respond to glandular therapy, and that menopausal symptoms are often alleviated by ovarian extracts. The obstetrician may well be grateful for pituitrin, and the surgeon for adrenalin.

Surgical achievements have contributed most fruitfully to both the clincial and experimental study of endocrinopathies, and ingenious operative procedures are constantly utilized to afford relief to patients with ductless gland disease. One need but mention thyroidectomies, sella decompressions, removal of ovaries, testicles, and hypernephromata. The pediatrician is frequently confronted with preadolescent disturbances of glandular function, and should be intimately familiar with the signs and symptoms of gigantism, childhood myxedema, status thymicolymphaticus, the several types of infantilism, and the pineal, adrenal and gonadal types of sexual precocity.

The dermatologist observes trophic disturbances of skin, hair and nails that are attributable to hypothyroidism, hypopituitarism, hypogonadism, or under-function of the chromaffin system. The neurologist and psychiatrist encounter instances of mental retardation, epilepsy, tetany, constitutional inferiority, psychosis and even mania that may have an endocrine explanation and subside under glandular therapy.

The cardiologist finds much to interest him in the tachycardia and arrthymias of thyrotoxicosis; the gastroenterologist realizes that an acute thyroid crisis may cause severe vomiting and diarrhoea; the metabolic expert is concerned with the chemistry of diabetes mellitus, diabetes insipidus and endocrine obesity.

Nor do the ramifications of endocrinology end even here. The administrator of public health is applying the results of endocrine research to the prophylactic eradication of goiter. The student of eugenics finds much to stimulate him in a consideration of inherited endocrine characteristics. It would require a lengthy recital to adequately acknowledge the debt we owe anatomists, physiologists, pathologists, pharmacologists and chemists, many of whom have vitally enriched our knowledge of the hormonopoietic system, and to whose continued researches we rightfully and confidently look for crucial aid in the solution of many endocrine problems.

There is no denying a broad horizon to this important field of medicine. Indeed, its fascinations have leaped the boundaries of our profession and today intrigue the laity. Unfortunately, as might be expected, the popular magazine and Sunday supplement have chosen, for the most part, those spectacular and least reliable features of the subject which could be calculated to appeal to the modern craving for the sensational. Hence it happens that the average layman's conception of the ductless glands centers embarrassingly around the organs of sex and their weird counterparts—"monkey glands," so much so that his newspaper acquaintance with "goats' glands" and "Black Oxen" forbid their association in his mind with such refined diseases as goiter and diabetes.

It behooves us, therefore, to be reasonably well informed as to the present possibilities, and perhaps even more as to the present limitations of organotherapy, and it is the endeavor of

this paper to summarize its present status, and to mention some of the hopes that we may legitimately entertain for its future.

DEFINITION OF ORGANOTHERAPY

The term, organotherapy, as used in this paper, refers to the therapeutic use of ductless gland substance for the alleviation of an endocrine disease. This restrictive definition at once excludes extracts derived from organs that are not at present considered members of the hormonopoietic system; such as bone marrow extract, brain substance, extracts of gastric or duodenal mucosa, kidney substance, liver substance, spleen substance and extract of tonsil or lymph gland. Indeed, Schafer, in the latest edition of his excellent work, "The Endocrine Organs," omits the thymus from the group of glands "to which we now commonly ascribe internally secreting functions," since no appreciable result is obtained from the removal of this organ, and since no reliable evidence has been presented that its extract has an "endocrine function" in the strict sense of that term.

Furthermore, organotherapy, as dealt with in this paper, does not include the use of ductless gland extracts for conditions or diseases whose incretory origin is uncertain or unlikely. *It is important, whenever possible, to make a clean-cut distinction between true specific supplementary substitution therapy for the relief of an incretory deficiency, and the administration of a ductless gland extract for its druglike pharmaco-dynamic effect.* Thus, the exhibition of thyroid extract in myxedema is an example of the former, whereas the injection of pituitrin to hasten labor is an example of the latter. It would be quixotic to diagnose hypopituitarism, merely because a phlegmatic uterus is stimulated to contract by pituitary extract. An injection of adrenalin may be a life-saving procedure in anaphylactic shock; it affords almost immediate though temporary relief from the intolerable urticaria of serum sickness; it shrinks mucous membrane when locally applied and is very useful, in operations under local anaesthesia, to diminish bleeding; its injection is a blessing to a patient in the throes of an asthmatic attack; but all these highly successful and desirable effects are pharmaco-dynamic, and do not signify the relief of an underlying adrenal deficiency. There must be no confusion on this point, if we are to evaluate properly the role of organotherapy in the treatment

of ductless gland disease. It is only fair to add that this distinction is not always possible. For example, we are not yet certain as to whether the remarkable, though transitory, reduction of thirst and polyuria in diabetes insipidus by injections of pituitrin is indicative of a pituitary origin for this disease, or whether the effect is a pharmaco-dynamic check upon a supposed metabolic center in a diseased hypothalamus.

It is axiomatic that a gland extract should never be administered when the corresponding gland of the patient is in a state of hyperfunction. No good can come from adding fuel to the flames. It would hardly seem necessary to mention so obvious a doctrine, were it not for the fact that some physicians still prescribe thyroid extract for goiter and pituitary extract for acromegaly, even though the goiter in question be toxic, and the acromegaly be evidence of hyperpituitarism. An unanalyzed syndrome is a quicksand for therapy.

Extracts of one gland are sometimes used to combat or antagonize excessive activity of another gland. Thus, Marine has reported favorable results from the administration of adrenal substance in cases of exopthalmic goiter; pituitary extract has been utilized for the same purpose (Solis-Cohen, Hector Mackenzie, Sir James Barr, etc.). Kate Knowles, in Kashmir, has treated osteomalacia with pituitary extract, upon the assumption that it would counteract an ovarian hyperplasia, which latter condition was supposed to be responsible for the excessive excretion of calcium. None of these procedures has received sufficient confirmation to warrant widespread use. They remain, for the present, interesting clinical experiments.

Our chief concern, then, is with that type of organotherapy which attempts to supplement a specific endocrine deficiency by supplying, from exogenous human or animal gland substances, that amount of hormone which the patient's diseased gland is unable to secrete; with the ideal purpose of having the endogenous patient's hormone plus the exogenous artificially administered hormone equal a normal amount of normal hormone.

CLASSIFICATION OF GLANDULAR PRODUCTS

How near have we come to reaching this goal with the commercial products at present available? A fairly extensive expe-

rience with modern glandular preparations leads me to classify their practical usefulness as follows.

CLASS A—*Includes those endocrine extracts which are standardized, strongly potent, uniformly reliable and specific; and which, when properly administered under appropriate circumstances, will yield consistent and convincing results.*

There are certainly two and possibly three such extracts; first, *thyroid extract or thyroxin,* as used in the treatment of childhood and adult myxedema and the milder grades of hypothyroidism; *second, insulin,* as used in diabetes mellitus to supplement a deficiency of pancreatic island hormone. *The doubt about the third extract, pituitrin,* an extract of the posterior lobe of the hypophysis, hinges upon the pituitary origin of diabetes insipidus. Its action in this disease is as specific as that of insulin in diabetes mellitus, and if diabetes insipidus is finally proven to be due to a hypofunction of the pars intermedia or posterior lobe of the hypophysis, then pituitrin will deserve to be grouped in Class A. The hormone, adrenalin, though standardized, potent and even synthetized, is not entitled to a place in Class A, since it has not, to my knowledge, been consistently or convincingly effective in the relief of the only adrenal deficiency syndrome that we are sure of, namely, Addison's disease. Its brilliant pharmaco-dynamic effects are not to be accounted for on the assumption that this synthetic hormone has compensated for a lack of endogenous epinephrin.

It is hardly necessary to comment on the value of insulin. Since its discovery and introduction, about two years ago, an amazingly rich literature has accumulated. It need only be emphasized that its very strength and specificity forbids any negligence in the accurate control of the diet of a diabetic. On the contrary, a rigid quantitative supervision is imperative, for overdosage with insulin is fraught with danger, unless promptly relieved by the administration of glucose.

The usefulness of thyroid extract in the treatment of childhood and adult myxedema, and its control by repeated estimations of the basal metabolic rate, is well established and remains one of the most brilliant contributions to medical therapeutics. No further comment on this score is necessary except again to call attention to the lamentable fact that most of these patients pass through the hands of many physicians before the correct

diagnosis is made. In 1920, Anders found that in 55 cases of myxedema collected from the American and Canadian literature, 74 per cent had failed of diagnosis by one or more physicians; this observation was reiterated by Hoskins in 1922. In 1924, at a meeting of The Association for the Study of Internal Secretions, Boothby stated that not one of the many cases of myxedema studied at the Mayo Clinic arrived in Rochester with a diagnosis of myxedema. At the University of California medical school we have had an exactly similar experience. In the majority of adult cases it is one of the easiest of diagnoses to make, and its repeated confusion (because of puffy eyelids) with Bright's disease is truly deplorable.

The milder forms of hypothyroidism are not so readily recognized, although the difficulties have been diminished by determinations of the basal metabolism. A moderately low (10 per cent to 25 per cent minus) rate will be found not infrequently. In instances where the clinical picture is suggestive, but the basal rate falls within normal limits, a therapeutic trial of thyroid extract, under careful observation, is justifiable and will occasionally yield gratifying results. The dictum that thyroid extract is contraindicated unless the patient's metabolic rate is below normal is no longer tenable.

The scope of this paper forbids consideration of the many "little signs" of hypothyroidism. It may not be out of place, however, to bring to your attention an interesting syndrome which I would term: *Adolescent Menorrhagia of Hypothyroid Origin.* A conversation with Slemons in 1922 first suggested the possible benefit to be derived from thyroid extract in certain cases of irregular and very profuse bleeding in young girls. A further study and analysis of this condition has convinced me of the existence of such a syndrome. In the absence of local causes within the pelvis, an early onset of menstruation (9 to 12 years of age) together with long continued and copious bleeding is very suggestive of hypothyroidism. Early maturity with early development of secondary sex characters are the dominant characteristics of this syndrome. There may be little else in the clinical picture to indicate deficiency of thyroid secretion. I am, of course, not referring to those remarkable examples of precocious puberty due to suprarenal cortex tumors, where development of breasts, appearance of pubic hair and onset of menstru-

ation may occur at the very early age of two to six years or thereabouts.

As a typical example of this menorrhagia of puberty I would cite the following case in a girl of 16 years, who began to menstruate at the age of 11½. Periods would occur at irregular intervals, but would last from six weeks to three months, and the flow on some days would be so copious as to require fourteen pads in twenty-four hours. There was nothing whatever in this girl's appearance to suggest hypothyroidism: skeletal growth, bodily proportions, weight, skin and facial appearance being quite normal. When I first saw her, in April, 1923, she had been flowing continuously, slightly or copiously, since Nov. 14, 1922, a period of five months. Her basal metabolic rate was 23 per cent minus. She was placed on thyroid extract (Armour) grains one daily, which was gradually increased to grains four daily. In June, 1923, her rate was 4 per cent plus, and in September, 1923, 9 per cent minus. She ceased flowing April 26th, ten days after beginning treatment. Subsequent periods occurred as follows: May 25-June 20, July 8-22, Aug. 9-22, Sept. 4-9, Sept. 26-30, Oct. 19-23, Nov. 10-14, Dec. 7-11, Jan. 4-8, and since then regularly every twenty-eight days for four or five days, the amount of the flow having become normal.

I venture to consider such evidence incontestable.

CLASS B—*Includes those endocrine substances which, in the hands of trustworthy clinicians, have produced remarkable improvement in specific deficiency syndromes, where the favorable response to the gland administered seems incontrovertible; but where such satisfactory results have not occurred with sufficient dependability or consistency to justify placing the extracts in Class A.*

There are three gland substances or extracts, in my opinion, which under particular forms of administration and in certain types of endocrine disease, warrant their inclusion in this Class B.

PITUITARY EXTRACT

Skeletal undergrowth is an outstanding feature of lack of anterior lobe hormone. Some authors, notably McGraw of Detroit in a recent careful study, have reported increased growth from oral administration of anterior lobe pituitary substance. Perseverance over at least a year's time is absolutely essential. Therapy over a few weeks or months is wasted time and money. My own experience has been encouraging in several instances, where it was stated that no growth had occurred for several years prior to instituting treatment, but the results have not been sufficiently spectacular to convince me that they could without question be ascribed to the gland therapy administered. Furthermore, Professor Evans of the University of California

has very kindly tested several of the commercial pituitary preparations on rats, both by feeding and injection, comparing the rate of growth of the treated animals with untreated litter mate controls under identical conditions. The results were entirely negative. These complete failures are to be contrasted with the remarkable gigantism he has produced in rats with an anterior lobe substance which he has prepared in his laboratories, but which is not yet available for trial on human beings. These important experiments will be referred to again later. *The commercial anterior lobe substances, therefore, in so far as stimulation of growth is concerned, probably do not deserve classification in Class B, and certainly not in Class A.*

A second important characteristic of hypopituitarism origination prior to adolescence is retarded sexual development, including: absence of secondary sex characters at an age when they should have appeared; and in girls late onset of menstruation with prolonged intervals and scanty flow; and in boys an infantile appearance of the external genitalia with absence of the prostate gland. To what extent does therapy with anterior lobe pituitary substance influence this syndrome? Occasional benefit has been reported and I have personally observed many instances which encouraged the belief that the gland administered had been responsible for the improvement noted. But here again we are confronted with the difficulty of being certain that the changes might not have occurred without treatment, especially in boys and girls treated between the ages of 11 and 15 years, a period when nature is apt to take command quite suddenly; and yet these are just the years when therapy should be undertaken if the boy or girl presents unmistakable signs of genital infantilism.

There can be no question, however, of the splendid results obtainable from anterior lobe and whole pituitary substance in post-adolescent hypopituitarism (without tumor). Especially gratifying and convincing is the effect produced in that not uncommon type of hypopituitarism in women between the ages of 18 and 35, which is characterized by rather sudden accumulation of a girdle adiposity, with gradually increasing intervals between menstrual periods and a flow so scanty as to require but one or two pads for the entire period; this not infrequently culminates in complete amenorrhoea.

A woman at the age of 32 years had a severe influenzal infection. She rapidly gained 75 lbs. and ceased menstruating. She came under my observation at the age of 37, having had complete amenorrhoea for five years. Her basal metabolism was normal. She received anterior lobe substance by mouth, fifteen grains daily, and menstruated one month later. Thinking she was cured, she remained away for three monthts and discontinued the medicine. She skipped three periods. Then she returned for further treatment. For the next six months she took anterior lobe (Armour) regularly, gradually reducing the dose from fifteen to six grains daily, and menstruated regularly and copiously.

Another woman gave a similar history, amenorrhoea beginning at the age of 26 years. Treatment was instituted when she was 32 years old, and the first period in six and one-half years occurred six months later; the next period occurred six months later, then one followed three months later, then two months later, and then five weeks later. She also lost 50 lbs. under treatment.

The writer has had many successful experiences in regulating the menstrual cycle to a twenty-eight or thirty day interval in girls and women, whose previous periodicity had varied from five weeks to three months. It would seem unduly critical to doubt the specificity of such glandular therapy, and therefore *anterior lobe substance is entitled to a place in Class B, in so far as its effect on post-adolescent aneoplastic hypopituitarism is concerned.*

A third important characteristic of hypopituitarism, both prior and subsequent to adolescence, is obesity. For the most part this adiposity is strikingly confined to the lower chest, intrascapular regions, abdomen and hips, and is conspicuously absent from the neck, upper chest, upper back, arms and legs, in cases unassociated with hypothyroidism. This type of adiposity is referred to as girdle obesity. If one not only records the weight but also the circumferential measurements at various levels, one will find at times a redistribution of this obesity (Beck) with but little loss of weight; and in most instances a loss of several inches around the waist, abdomen and hips, under pituitary therapy. It is true that in many cases better results are achieved if thyroid extract is combined with the pituitary substance. It must not be inferred, however, that the reduction so obtained is entirely due to the thyroid extract, and that the pituitary factor is negligible or imaginary. Beck, Timme, Englebach and Tierney and the writer have all obtained reductions that seem incontestable. *In a recent paper on endogenous endocrine obesity I have referred to several cases in which a loss of 20 to 50 lbs. was secured by pituitary extract alone.* I am

inclined to believe that success is more likely if the pituitary substance is prescribed in tablets or capsules that are coated with salol, on the assumption that more unaltered absorption takes place from the intestines with less likelihood of harm from gastric acidity.

In this connection I might mention a recent conversation with Professor Evans in which he divulged the disappointing news that neither pituitrin (extract of the posterior lobe) nor his anterior lobe extract reduces the adiposity of partially hypophysectomized rats. This suggests one of two conclusions, either that the adiposity is partly of cerebral and not purely pituitary origin (as claimed by Camus and Roussy and Bailey and Bremer), or that the otherwise potent pituitary extracts of Evans do not contain the fat-reducing hormone. *It is the uncertainty of this situation experimentally, and the inconsistency of clinical results, which prompts the writer to place whole pituitary substance, as a fat-reducing extract, in Class B, rather than Class A.*

TRANSPLANTATIONS AND IMPLANTATIONS OF TESTICULAR SUBSTANCE

The commercial preparations of desiccated testicular substance for oral use, and the liquid extracts for injection purposes are probably almost inert. To quote one of the foremost endocrinologists, Falta, "The drug therapy of sexual glandular insufficiency has as yet had in man no decisive results. The feeding with testicular substance is but little carried out, and the reports as to the result of injection of sexual glandular extracts disagree. Spermin (Poehl) may have a certain stimulating action on the nervous system, but profound symptoms of insufficiency are hardly improved thereby." The testicular products, therefore, obtainable from manufacturing firms, are not entitled to a place in Class B, let alone Class A.

The world-wide interest in sex gland transplantations and implantations, however, cannot be brushed aside merely because of the sensational appeal involved. Unquestionable and remarkable improvement has been obtained in many instances of early and late eunuchoidism, and the evidence presented will withstand scrutiny. Not only have there been extraordinary transformations in the subjective sphere, such as increased energy, feeling of well-being, greater capacity for work and return of

libido, but what is far more important and reliable in judging the efficacy of a therapeutic agent, striking objective changes as well, such as increased size of genitalia, growth of hair, changes in weight and alterations in skin and nails.

Dr. Nixon, associated with me in the Ductless Gland Clinic, published the following case. A boy of 18 years, six feet one inch tall and weighing 197 lbs., came under our observation because of lethargy, weakness, inability to work or concentrate, and momentary attacks of unconsciousness (petit mal). He was tall, fat distribution was markedly feminine, including broad pelvis, mammary fat and mons veneris padding; he had shaved only three or four times; pubic hair was of feminine type, and voice was still high pitched. Basal metabolism was normal. He received three implantations, three months apart, of fresh semi-solid untreated ram's testicular substance, forcibly injected into the abdominal wall. This testicular material was obtained through the courtesy of Dr. Stanley, and the method of implantation followed exactly the procedure first suggested by him. The change from a whining, lackadaisical, effeminate boy to a vigorous, upstanding young man earning his living was so marvelous that I would have suspected some psychic magic if it were not for unmistakable evidence, such as loss of 25 lbs., growth of beard and change of voice.

I have recently recorded a case of onychauxis in a eunuchoid (whose gonad insufficiency dated from direct trauma with subsequent sloughing of the testicles), in whom the rough-ridged shell-like appearance of finger and toe nails changed to smooth, normal nails after testicular implantations. Photographs of the nails before and after treatment were published as proofs.

More extensive clinical studies may be found in the writings of Steinach, Lichtenstern, Lespinasse, Lydston, Thorek, Stanley, Vecki, and others, which prove beyond question that *strikingly beneficial results are often obtained by transplantation or implantation of human or animal (usually monkey or ram) testicular substance into boys and men who are victims of hypogonadism. This judgment is not to be construed as applying to the same procedure when used in Ponce de Leon strivings for rejuvenation or longevity, the premature exploitation of which does not redound to the credit of some members of our profession.* Testicle implantations for testicle deficiency have yielded positive results sufficient to justify classifying this substance, when thus administered, in Class B.

OVARIAN PRODUCTS

It is rather odd that we still know so little concerning the clinical attributes of ovarian dysfunction. Since menstruation must be intimately associated with ovarian function, we have, rather crudely, concluded that hyperfunction must result in excessive uterine bleeding or menorrhagia, and that hypofunc-

tion culminates in amenorrhoea. As a matter of fact, excessive menstruation (when not due to infection, polyp or tumor within the pelvis) is probably due to hypothyroidism and only secondarily to ovarian disturbance; and amenorrhoea is more often primarily dependent on hypopituitarism and only secondarily on a deficient ovarian secretion. It is, furthermore, surprising that despite the wholesale ovarian castrations of the past fifty years, our knowledge of the clinical consequences is relatively meager, being confined largely to three phenomena: vasomotor symptoms, amenorrhoea and obesity. Extreme hypofunction of the ovaries prior to puberty is supposed to permit the anterior lobe of the pituitary to run rampant as it were, resulting in tall eunuchoid giants, with marked disproportion between the long extremities and relatively short trunk. It is also supposed to produce a certain type of localized adiposity confined to trochanteric fat pads. Menstruation either does not occur at all, or is late in onset.

To what extent can these disturbances be rectified by ovarian extracts? There is no lack of ovarian preparations on the market, both for oral use and injection, consisting of the whole ovarian substance, corpus luteum extract, and an extract of the material that remains after removal of the lutein tissue, called ovarian residue. *It would appear, accordingly, that there must be definite indication for the use of either lutein, ovarian tissue without lutein, or the entire gland, whereas the notions of most of us in regard to such distinctions are exceedingly vague and confused.* The writer's experience coincides with that of Novak, whose appraisal of ovarian therapy in 1922 applies equally well to the situation at the end of 1924. The gist of his conclusions can be summarized in the statement that *the indications for ovarian therapy are still ill defined, and that the commercial products available have achieved but little in a quarter century of trial, beyond a very definite relief of the vasomotor symptoms of the menopause.* And it may be noted with reference to the last item, that the earlier the artificial menopause, the more aggravated the symptoms and the less efficacious the ovarian tablets, capsules or ampoules. There will be many to disagree with this lugubrious view of ovarian therapy, but it may be accepted as a general rule that there is far less enthusiasm shown in reporting failure than in recording success. At the same time I freely

confess that I have used and still use ovarian preparations, and have occasionally achieved surprising results, especially in the relief of different sorts of subjective symptoms, but the magic powers of "the glands" have seemed more convincing to the patient than to me. *In so far as the alleviation of menopausal symptoms is concerned, ovarian extracts deserve classification in Class B.*

OVARIAN TRANSPLANTATIONS AND IMPLANTATIONS

It is curious that far less interest has been manifested in ovarian implantations than the corresponding procedure in the male sex, despite the fact that ovarian castrations are infinitely more common than testicular castrations. I have not had any personal experience with this procedure, but plan to use it shortly. Falta cites the two following cases:

"Cranner transplanted into a twenty-one-year-old girl, who had never menstruated and who possessed rudimentary mammae, the ovary of an osteomalacic woman. Menstruation then set in and the breasts developed. Still more remarkable is the case of Halliday-Crom. In this case amenorrhoea had set in after labor and symptoms of absence developed. The small cystic ovaries were removed and a foreign ovary implanted. The woman again menstruated four months after the operation, and four years after the operation she conceived and bore a normal child. This case was earnestly discussed before the Edinburgh Obstetrical Society, and can not well be denied. There is, indeed, in this case no doubt that if there has been no error of observation, this woman bore the child of another woman. Serious objections might be raised against such procedures on ethical and forensic grounds.

"Sippel reports from Bumm's service four cases in which previously sterile women conceived and passed through a normal pregancy after the sluggish function of the otherwise normal ovary had been roused and speeded up by transplantation in the abdominal wall (prevesical space) of two disks of ovarian tissue still warm from the body of another woman. These grafts were taken from women being hysterectomized for cancer, myoma or pulmonary tuberculosis."

These results are so striking that further trial of this method of ovarian therapy seems advisable, although great caution should be exercised in the selection of the ovarian tissue to be grafted. It at least constitutes an immense advance over the indifferent results ordinarily obtained from the present commercial products.

We have now given consideration to the practical usefulness of insulin, thyroid, pituitary, ovarian and testicular extracts.

CLASS C—*includes all other endocrine extracts at present available, where it is conceded that occasional benefit may have been obtained from their employment in a variety of conditions;*

but only infrequently and as yet insufficiently to justify their use in general practice. In this group belong parathyroid, pineal, adrenal, thymus, prostate, mammary and placental extracts. We are not even certain that the pineal, thymus, prostate, mammary and placental organs are really incretory glands.

The above classification is based largely on my own personal experience, second on a reasonable acquaintance with endocrine literature, and third, on questions and answers in conversation with some of the leading endocrinologists of this country. The above statements hold as my views for Nov. 13th, 1924. They may be altered in the near future. We are on the threshold of great discoveries. Pancreatic extracts belonged in the Class C of inert extracts until Banting's brilliant discovery of insulin promptly advanced them to Class A. Evans may do the same before long for the anterior lobe of the hypophysis, and Allen and Doisy may shortly perform an equal service for ovarian extracts.

FUTURE PROSPECTS AND METHODS OF PROGRESS

Researches in pure science abound in fruitful possibilities whose practical translation later into endocrine investigation or therapeutics may astonish the original worker. Such occurrences cannot be systematically planned nor foreseen, but the alert investigator is constantly on the lookout for new methods in related sciences which may be applied to his own field of endeavor. It may seem a long way from the chemist in his laboratory to the clinician in his office. Unfortunately they are often farther apart than they should be. To what extent can the general practitioner and the specialist in their daily work "by the bedside" contribute to our knowledge of organotherapy? Their opportunities are great. Many of the most stimulating and important discoveries in endocrinology emanated from the clinic. One need but recall a few names out of a great number, such as Addison, Graves, Basedow, Moebius, Murray, Gull, Kocher, Marie, Halsted, Plummer, Cushing.

Precise observations, carefully controlled, may constitute data from which valuable conclusions may be deduced. The subjective rôle, both on the part of physician and patient, in judging the efficacy of any treatment, is a formidable one. This makes it all the more necessary, if one's reasonings are to possess

any merit, that one employ *"the one thing at a time" type of treatment.* This should be a fundamental principle in glandular therapy, at least among those clinicians who desire to record their experiences for the benefit of their colleagues. No sensible deductions can be made concerning any one drug, if several are administered simultaneously. It may be argued that the great majority of physicians are not publishing papers, and are only interested in "results."

PLURIGLANDULAR THERAPY

Let us briefly examine this *pluriglandular three-ring circus.* It is granted at once that functional upheaval in any one gland of the hormonopoietic system does not ordinarily permit of normal function in the remainder, but frequently involves one or more of them in its tribulations. But, as Sharpey-Schafer phrases it, "our knowledge regarding this is still in many respects confused." *In the enthusiasm for roping these glands together, a veritable jungle of knots has been tied that is difficult to untangle.* The doctrine of pluriglandular disease has naturally led to the doctrine of pluriglandular therapy, with the introduction of "shotgun hit-or-miss mixtures." There is a marked tendency these days to hide behind the skirts of this so-called interrelationship. *As a matter of fact, the majority of endocrinopathies which we are justified in diagnosing exhibit a predominantly uniglandular basis, which anyone properly trained in endocrine diagnosis should be able to recognize.* A firm foundation for incretory therapy demands a sharply defined analysis of the symptoms and signs, with emphasis on the gland primarily responsible.

Even if it be conceded (which of course it is) that serious disease of one gland will produce disturbed function in one or more other glands, then logic should force the conclusion that a restitution of that first gland to normal function will, ipso facto, restore the remainder to normal function. Indeed, there is experimental proof for this contention. As a result of hypophysectomies in rats and tadpoles, Evans and Smith have demonstrated alterations in thyroid and adrenals; these latter abnormalities have been corrected by replacement therapy with anterior lobe substance, without any recourse to thyroid or adrenal extract.

At any rate, if one prescribes one gland extract and watches its effects over two or three months or until no further effects are obtained, and then keeping its dose the same, adds another gland extract, clinical changes that subsequently occur may then with some logic be ascribed to the second gland administered. In this manner one may individualize one's therapy. Objection is sometimes made that this involves a waste of time when a pluriglandular mixture might have been used at the outset; as if time were any object in a type of therapy that must be continued for years. Myxedematous patients must take thyroid for life; insulin would have to be given indefinitely, if the "load" were not reduced by regulation of the sugar formers in the diet; pituitrin must be administered continuously, as a rule, in diabetes insipidus.

In any event, one can compound one's own mixtures for the individual case if one understands endocrinologic diagnosis and is acquainted with proper dosage; and if one is not familiar with both these fundamentals one should not use stock formulas. One might as well expect a dermatologist to remove a brain tumor, the only difference being that little harm comes from the use of these commercial combinations, since most of the constituents are impotent. *Fortunately, the stampede into the "endocrine gold fields" (as merrily phrased by Abel) is beginning to wane, probably because much of the ore is low grade. One of the best methods of judging the potency of an endocrine extract is to study the effects of overdosage.* An excess of thyroid extract produces unmistakable signs and symptoms of thyrotoxicosis, which should be familiar to everyone. One dare not be careless in overdosing with insulin. Excessive amounts of adrenalin and pituitrin produce annoying symptoms. We may well ask what similar alarming or dangerous symptoms are produced by very large doses of whole pituitary, anterior lobe pituitary, ovarian, testicular, parathyroid, pineal, adrenal cortex or thymus extract; probably none beyond headache or nausea!

IMMEDIATE PROSPECTS

The brilliant discoveries of the future in endocrine therapeutics will probably have their origin in elaborately planned, well endowed experimental investigations in which physiologists, chemists, pathologists, pharmacologists, biologists and clinicians

co-operate intensively. It was that sort of group attack by Kendall, Mayo, Plummer, Wilson and Boothby that produced thyroxin; it was a similar effort by Banting, Best, Macleod, Collip and co-workers that achieved insulin. What is the present outlook for further results of like importance and unimpeachable character?

Professor Abel of Johns Hopkins, in his admirable Harvey Lecture, recently published, reviews the work of himself and associates in the isolation of the active chemical principle of the posterior lobe of the pituitary. This principle has been isolated in the form of a tartrate for which no claim is yet made as to chemical purity or individuality, but which "possesses extraordinary potency as a smooth muscle stimulant, being 1000 to 1250 times more powerful than the acid phosphate of histamine, a base which has hitherto held the ranking position in this respect." He submits proof that this tartrate "displays all of the characteristic physiological properties of a good aqueous extract of the posterior lobe of the hypophysis. In addition to its action on the uterus, it causes a prolonged rise in the arterial pressure, with constriction of the peripheral arterioles and capillaries, a brief diuresis in the green-fed rabbit, has an antidiuretic action in diabetes insipidus, and affects the respiration of dogs and rabbits in a characteristic manner." Moreover, *these brilliant researches of Abel bring strong evidence to the support of the hypothesis that the posterior lobe has an endocrine function and that it elaborates a specific hormone which controls the removal of water from the body via the kidneys and perhaps other organs, and that a deficiency of this hormone leads to a polyuria or diabetes insipidus.*

The remarkable work of Evans, Smith and associates of the University of California, also partly summarized in a Harvey Lecture shortly to be published, holds great promise for a powerful extract from the anterior lobe of the hypophysis. This extract, prepared fresh from bovine hypophyses, is now protein-free and sterile. Its concentration for clinical purposes remains to be accomplished. Its use at present would be too costly, since very large quantities would be necessary to reproduce the results in human beings experimentally attained in tadpoles and rats. The intraperitoneal injection of this anterior lobe extract brings to normality the four deficiencies that result from hypophysec-

tomy in the tadpole, in that it accelerates the growth rate; induces a normal depth of pigmentation; repairs the atrophic thyroid and interrenal bodies, the specimens metamorphosing; and reduces the fat organ to normal dimensions. The normal and thyroidless tadpoles, when injected with this anterior lobe extract, show an acceleration in their growth rate, attaining an unusually large size, and display an increased depth of pigmentation. The dwarfism of hypophysectomized rats is corrected by injections of this extract; and the secondary alterations in other endocrine organs are alleviated. No effect, however, has been obtained as yet on the adiposity that results from hypophysectomy in rats. Injections of this anterior lobe extract into normal rats produces gigantism consistently, a truly brilliant achievement.

Allen and Doisy of St. Louis have succeeded in preparing an ovarian hormone from the liquor folliculi of hog ovaries. This follicular fluid has been rendered protein free. Injections of this extract into spayed animals (rats and mice) produced typical estrual hyperemia, growth and hypersecretion in the genital tract, and growth in the mammary glands. They concluded that this hormone seems to be an efficient substitute for the endocrine function of the ovaries of the non-pregnant animal. Furthermore, these spayed animals, when in a condition of artificially produced estrus, would exhibit typical mating instincts, successful copulation occurring, which justified the conclusion that this follicular hormone is the cause of estrual or mating instincts, since these animals will only copulate in estrus. Injections of this extract into animals immediately after weaning hastened sexual maturity. These crucial results could not be duplicated by commercial extracts of ovaries, corpora lutea, and ovarian residue, from three of the largest firms manufacturing biologic products. Allen, in a paper before the Association for the Study of Internal Secretions, in June, 1924, announced that this follicular hormone was being tried clinically on a few women whose ovaries had been removed but in whom the uterus had been left intact. Clinical use on a large scale was still impractical because of the very large quantities necessary. The problems of concentration were yet to be overcome.*

* Since this paper was written, Collip has announced the preparation of a parathyroid extract which seems to control the calcium content of the blood.

In these three great discoveries of Abel, Evans and Smith, and Allen and Doisy, lie our immediate hopes for a more successful organotherapy with pituitary and ovarian extracts. Undoubtedly undertakings of similar magnitude will soon be under way for other important glands of internal secretion, whose extracts at present leave so much to be desired. Great difficulties and obstacles will be encountered, baffling complexities will demand solution, discouraging delays are to be expected. It took thirty years of persistent endeavor by many scientists in many lands, from Minkowski in 1892 to Banting in 1922, before insulin was consummated. Meanwhile we must work with what we have. It is hoped, in the attempt to evaluate what we have to work with, that the writer has displayed neither ignorant credulity nor cynical intolerance. In endocrinology we have had too much of both.

THE DIAGNOSIS AND TREATMENT OF HYPO-OVARIANISM*

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Occasionally, "ovarian" feeding seems to produce truly wonderful results. They are wonderful to the patient because she has usually learned the futility of all other remedies, and wonderful to the physician because he cannot explain how the treatment acts, nor how so many apparently unrelated conditions can be favorably affected by the same agent. Nevertheless, experience apparently shows, as illustrated in the case histories narrated below, that such widely differing disturbances as constant and severe headache, or a psychosis, or high arterial tension with its annoying or dangerous complications, or a very troublesome constipation, may each be entirely relieved by this peculiar and almost incomprehensible form of organ therapy. In other words, the symptoms of a possible ovarian deficiency are so often obscured by neuroses which give no suggestion of the primary disorder that there is great need of pointing out a few indications to guide the treatment. In addition to the difficulties in diagnosis in these cases, there are also the uncertainties in both the mode of administration and the character of the medicament.

The study, of which this is a brief outline, began with an investigation of the available ovarian preparations, and, because of the very practical therapeutic problems involved in double oöphorectomy, has been confined at the outset to derivatives of the entire gland substance. The possible sources from which "active material" may be obtained are, of course, the ovarian follicle with its serous fluid, the corpus luteum, and the interstitial ovarian cells. For a test to determine the comparative potency of these substances or their extracts we first employed the acceleration or retardation of the guinea pig's oestrus, as described by Stockard and Papanicolaou.†

* From the Johnston Livingston Fund for Experimental Biochemistry, Cornell University Medical College, New York.
† Am. J. Anat. (Phila.), 1917, 22, 225.

The extracts tested were given by mouth or by injections. As a rule, injections act in a more effective but less uniform way than when given by mouth. The mouth administration, though milder in action, produces a certain stimulating effect, which is revealed by an activation of the oestrus processes. Among the different types of mouth extracts tested (neutral, alkaline, acid aqueous, alcoholic and glycerin) the glycerin type seemed to give the most uniform results. A further report on this work will be published later by Dr. Papanicolaou, who made most of the biological tests.

Because of these findings, we have employed a glycerin extract of the whole pig ovary. That particular animal was chosen because its glands contain in greatest abundance and most constantly all of the possible sources of active material. Glycerin as an extractive material presents many advantages. It is an entirely neutral medium which introduces no changes by the presence of acidity or alkalinity. It disrupts the envelopes of the cells and then takes up all of their water soluble and a considerable proportion of their lipoidal contents and includes the nucleoproteins, globulins and albumins. A glycerin extract of the thyroid, by the way, was the first substitute employed for "fresh" gland feeding, and it gave very satisfactory results, but was later abandoned because it readily decomposed. Desiccated products were then introduced, but these present many obvious disadvantages. The drying of an entire organ includes much foreign material, especially fat which, to facilitate the drying process and to prevent decomposition, is ordinarily removed. "Defatting" excludes the lipoids from the medicament and so may change its natural characteristics and alter its effects. The subsequent drying introduces the possible or probable changes produced by autolysis or putrefaction. The feeding of fresh gland tissue is generally believed to come the closest to the ideal of a true "substitution therapy." But for general use fresh glands are impracticable. The nearest approach to this method is probably a standardized glycerin extract made from as fresh material as can be obtained. For these theoretical reasons, and because it seemed to show the best results in the oestrus tests, we selected it for repeating Dixon's experiments. He has reported* a marked increase of "pituitrin" in the spinal fluid after the

* J. Physiol., 1923, **57**, 129.

injection of certain ovarian derivatives. It is a difficult and complicated test, but seems quite definite. A glycerin extract of the entire fresh pig ovary is apparently very constant and potent.* Furthermore, the effects of this material, when given by mouth, were also very clear. After its intravenous injection a large amount of "pituitrin" is demonstrable in the dog's spinal fluid within fifteen or twenty minutes. After administration by a tube through the mouth into the stomach (of the anaesthetized animal) the pituitrin does not appear in the spinal fluid until after the elapse of a much longer period. But it is then demonstrable in a considerable amount.

The follicular fluid, the corpus luteum and the interstitial cells all give this reaction, but extracts of the entire gland seem to be the most active. A detailed report of this work will soon be published. It is enough at present, however, to state that a glycerin extract of the whole fresh pig ovary, when administered by mouth, not only produces a demonstrable effect upon the guinea pig's oestrus, but also produces a demonstrable amount of a material in the dog's spinal fluid which gives the reactions of pituitrin.

It is reasonable, therefore, to infer that functional activity of the ovary stimulates functional activity in at least the posterior lobe of the pituitary and, conversely, that ovarian failure might cause a pituitary deficiency. In other words, ovarian feeding, as indicated in our dogs by Dixon's test, should stimulate the activity of the pituitary.

There is, of course, little or no knowledge of the mode of action of the endocrine glands, and still less of the manner in which these organs when fed by mouth can produce their undoubted effects. The clinical results, however, need some explanation, if only to aid in the selection of the best form of the medicament. The feeding of a "fresh gland" may, after its digestion, supply that gland's active principle. It is much less probable that any desiccated product, especially after it has been defatted, can accomplish this object. It is more reasonable to believe, however, that after the passage of the ingested material through the gastrointestinal tract and the liver there enters the circulation some "activating substance" which may

* The chemical and the physiological tests required were made by Nathan F. Blau, Ph.D.

be an antecedent of the gland's active principle. This activating substance can be supposed to facilitate or promote the parent gland's nutrition by attracting to it the most needed foodstuffs. It can be imagined to functionate like an opsonin, which attaches itself to the gland's epithelial cells and conducts into them the circulating materials which they most require. It thus activates both anabolic and katabolic metabolism, and so should increase the quantity of the defective organ's product.

If the vitality of the defective epithelium is not too much impaired, the activation of its nutrition should also improve the quality of the gland's product. In the case of the thyroid, at any rate, there is a growing suspicion that the quality of its secretion may be as important as its quantity and, clinically, there are many cases of apparent hyperthyroidism which seem to be benefited and not injured by thyroid feeding. The activating substance which is supposed to enter the circulation after the ingestion of an endocrine gland, or its derivative, must also be closely related chemically to that gland's "active principle," because, both experimentally and clinically, it performs some but not all of the functions of the patient's natural product. No amount of ovarian feeding, for example, can restore the menstrual phenomena after they have once been abolished by double castration. Nevertheless, ovarian feeding in these cases can relieve many other abnormalities and actually (in dogs) seems to stimulate the pituitary.

While these experiments were in progress a number both of male and female dogs were subjected to double castration, and the simultaneous removal of one thyroid lobe. Five months later the remaining lobe was excised and found to have gained much more in its iodin content than that of the control animals, or some 200 to 300 per cent. There is thus, as is clinically quite apparent, some demonstrably close relationship between the thyroid and the ovary.

There are many experiments which show a relationship between the thyroid and the pituitary, and Evans, in his work upon tadpoles, seems to prove that it is one of mutual stimulation. The thyroid is also generally believed to vigorously increase, probably through their autonomic or parasympathetic nerve supply, both the secretory activity and the motility of

the gastrointestinal tract. In general, it apparently accelerates throughout the body all metabolic activity.

As regards the ovary, it is possible to infer, because of the storage of iodin in the thyroid after castration, that ovarian activity and so ovarian feeding with a glycerin extract promotes the normal functionation of the thyroid and, through the thyroid, the normal functionation of the gastrointestinal tract. Also, according to Dixon's test, the same conditions or treatment can promote the normal functionation of the pituitary and thus could increase peristalsis and uterine contractions. It is, therefore, quite obvious that many of the neuroses or the symptoms which seem to be the result of hypothyroidism or hypopituitarism, especially in the digestive tract, may really originate in a hypoovarianism. Fortunately, the abnormalities in the menstrual function may give the desired clue. This has to be followed by an exclusion of the other possible causes of trouble, but the final "proof of the pudding" all too often has to rest upon therapeutic experimentation.

When the thyroid is chronically underactive, the general condition is one of asthenia, accompanied by a more or less striking pallor and an obvious deficient activity of all the other organs. When this gland is overactive there is a prevalence of the opposite conditions. The extreme cases of deficient or excessive thyroid functionation are represented by cretinism, or myxedema, or by exophthalmic goitre.

The next organ to be considered is the pituitary, which, through its output of "pituitrin" into the spinal fluid and thence into the circulation, is well known to stimulate, particularly, intestinal peristalsis and uterine contractions. It may thus, clinically, have more or less to do with either constipation or profuse or perhaps irregular menstruation. The signs which may indicate chronic inactivity on the part of this gland are extremely vague, but sometimes include frontal or temporal headache. The more pronounced, or congenital, cases are supposed to result in defective general development, especially of the genitals, or, in extreme cases, the peculiar configuration known as Froelich's syndrome.

Chronic overactivity of the pituitary is believed to be represented in some forms of giant growth, especially of the face, hands and feet, as shown in acromegaly.

The little that is known of the physiology of the ovary outside of its apparent stimulation of the pituitary is confined practically to gestation and to the menstrual phenomenon. The supposed relationship of a deficiency in the corpus luteum to the liver and so to the vomiting and toxemias of pregnancy is exceedingly problematical and, clinically, the administration of derivatives of this material are very uncertain in their effects.

In short, knowledge of ovarian physiology is limited almost entirely to clinical observations upon the neuroses of the menopause and to the changes which occur, especially in young women, after double oöphorectomy. The most prominent symptom after the loss of the ovaries is, of course, the prompt cessation of menstruation or, if traces of the gland remain, as is not uncommon in cases of suppuration, its decrease in amount or gradual disappearance. When the amenorrhea is complete and immediate, it has been incapable of restoration by feeding any derivative of the ovary.

As a rule, the younger the subject the worse are the results of the castration, and this should be true from what is now known of the stimulating effect of the ovary upon the pituitary, and of the latter upon the thyroid. For there is little doubt that normal growth and development are very dependent upon the functional integrity of both these glands, and if either one fails, as it should in the absence of the ovary, there may follow almost any abnormality. It remains true, however, that ovarian feeding, to be *completely* successful, seems to require the presence of at least some living ovarian tissue. Nevertheless, expeence shows that when this is undoubtedly absent much help for the other and more distressing disturbances than amenorrhea can thus be given.

The ingested material, after its entrance into the circulation, both experimentally and clinically, although it cannot restore the absent menstruation, is apparently capable of stimulating the pituitary and probably the thyroid and through other as yet unknown organs, may prove extremely valuable.

This means that amenorrhea in itself is comparatively unimportant, but when it exists before the natural menopause in the presence of otherwise unexplainable symptoms the latter can often be benefited by the right kind of ovarian feeding. Whether the word "often" can be changed to "regularly"

depends upon the acumen of the physician and his ability to weigh the significance of the frequently conflicting signs. These have reference chiefly to the rather vague and uncertain evidences of pituitary deficiency, such as frontal or temporal headache, or constipation, or some abnormality in growth or development. The others, such as simple hypertrophy of the thyroid, or defective gastrointestinal functionation, especially if accompanied by asthenia, suggest hypothyroidism. The final test is really a therapeutic experiment, but it is legitimate because entirely harmless, and the results are as speedily apparent as any "specific" treatment.

Another menstrual abnormality which seems to indicate deficient ovarian functionation and suggests that ovarian feeding may prove successful is functional dysmenorrhea. The experimental data which point towards a local deficient nutrition and so towards hypoovarianism in this peculiar and very common neurosis are supplied by the astonishing results quite frequently obtained by ovarian feeding alone. This, to be sure, is a very insecure foundation upon which to build a theory, but it is the best at present available. Apparently, for unknown reasons, or perhaps from defects in the general condition, like sepsis, the ovary becomes impaired in its vitality and so lacks the power to absorb the nutriment which is needed to enable it to perform its normal function. At the menstrual period then, or when the gland is supposed to be most active, it becomes congested in an automatic but ineffectual attempt to obtain the requisite nutriment, and the pain is the result of the pressure of the blood in the unexpandable ovary. Ovarian feeding relieves the local symptoms because it, presumably, supplies in abundance the requisite activating substance and so obviates the need of the congestion.

If this theory for hypoovarianism can be accepted, ovarian feeding should also relieve symptoms which do not have such an apparently direct causative relationship to a defective ovary. For the ingested material not only may improve the nutrition and functional activity of this gland, but evidently stimulates at least the posterior lobe of the pituitary and also, though less definitely, the thyroid. The uncertainties in diagnosis are still great, but the inclusion in the symptoms of signs of an accompanying hypopituitarism or hypothyroidism often places the

complaints apart from the products of a disordered imagination.

In addition to the actual pain of menstruation, the more common and distressing accompanying neuroses which may be the result of hypoovarianism include violent headache, or migraine, or dizziness, or insomnia, or gastroenteric disturbances, or pronounced exacerbations of almost any pre-existing abnormality. If the ovarian feeding relieves the dysmenorrhea, it is almost always of more or less benefit for the concomitant difficulties.

It is impossible, at present, to explain exactly the mode of action of the medicament, but experience seems to prove that its effect is at least more than psychic. Because of the relationship of this gland with the thyroid and pituitary, and because, clinically, some cases of amenorrhea or dysmenorrhea can be relieved better by feeding either of the other two organs rather than the ovary, it is legitimate and often necessary to experiment cautiously with each of these organs, or with a combination of ovary and thyroid, or of ovary and pituitary.

Functional menorrhagia and metrorrhagia, or an excessive or an irregular menstrual flow without any demonstrable organic change, because of their frequent occurrence during the menopause, are undoubtedly associated with some hypofunctionation of the ovary. But the existing knowledge of the mechanism of these abnormalities is as vague as that about dysmenorrhea. There are a few rather indefinite facts which point to an active principle in the corpus luteum, and another with a different function in the interstitial cells. Eventually, it may be found that one inhibits and the other stimulates the menstrual flow. But until these possibilities are more clearly determined, functional menorrhagia and metrorrhagia can be regarded as indications of some form of hypoovarianism. Consequently, the feeding of preparations of the whole ovary is, at least, worthy of trial.

SUMMARY

The practice of ovarian feeding for every imaginable and imaginative female complaint is very costly to the credit of the physician and to the purse of the patient, and should be restricted to conditions in which there are at least some reasonable hopes of relief. These hopes, which as yet can with diffi-

culty be dignified as definite indications, are based almost entirely upon the existence of amenorrhea or dysmenorrhea, or of menorrhagia or metrorrhagia, or only upon abnormalities in the menstrual phenomena. The most definite and reliable is amenorrhea, and for diagnostic purposes it need not be complete. Unfortunately, this symptom apparently is not always due to a primary ovarian hypofunction or hypoovarianism, but may be secondary to some systemic failure, and that is more commonly traceable to hypothyroidism than to any other one cause. Only after all other origins are excluded, and this may be possible only after cautious experimentation with thyroid feeding, can the amenorrhea be traced to hypoovarianism, and then the cessation of menstruation in itself is seldom a legitimate complaint. Indeed, the chief difficulties often appear to bear no relationship to the ovary and can only be causally connected with that gland by exclusion or by the elimination of whatever is known of other pathological physiology. The final decision has to be reached by a comparison of the few facts which have been established for the action of the pituitary and for that of the thyroid and for what may occur after double oöphorectomy.

One chief, or cardinal, symptom which points towards ovarian hypofunctionation is, then, amenorrhea. It may be complete or "incomplete," but underactivity of the entire gland should not cause an excessive menstrual flow.

Our knowledge about functional dysmenorrhea, if it can be called knowledge, is much less definite than about amenorrhea, and is based entirely upon clinical observations, and chiefly upon those instances in which relief of the pain after ovarian feeding is complete. Dysmenorrhea, unlike amenorrhea, often, if not always, itself requires treatment and is easy of recognition. But its presence in association with other neuroses which may be much more serious is of great clinical value. The local pain seems generally, though not always, dependent upon defective ovarian nutrition and hypofunctionation is therefore presumable. This can be supposed to cause defective activity on the part of the pituitary or the thyroid, and the pituitary quite definitely and the thyroid probably can receive stimulation through ovarian feeding. Just how the commoner neuroses like headache or gastrointestinal disturbances can thus be relieved is unknown. It is probably not direct, however, but

through the influence of the ovarian product upon other secretory or nutritive organs. Not infrequently there will be encountered some neurosis in which the cause seems unexplainable. But a careful history may reveal a long past period of amenorrhea or dysmenorrhea, and either of these may give the desired clue.

The reasons for combining ovarian with thyroid or pituitary feeding are quite obvious. They seem to each reinforce what little is known of the function of the other and, practically, a much better result may be obtained by a combination than by the use of ovarian feeding alone. Furthermore, too prolonged or too intensive treatment with the ovarian derivatives sometimes is followed by nausea or gastroenteric disturbances, and these are apparently prevented by a simultaneous but cautious use of thyroid.

The available "knowledge" of the subject suggests rather than proves that menorrhagia and metrorrhagia are, at least before the menopause, not regularly the direct result of hypofunctionation on the part of the ovary. During the menopause, however, menorrhagia and metrorrhagia are common, and may result from deficient ovule formation, although the results of oöphorectomy are against this possibility.

When more is known of the function of the interstitial cells, these menopause disturbances may be better explained. But until then menorrhagia and metrorrhagia can be said to be indications for ovarian feeding only during the menopause. They suggest in earlier ages a primary pituitary rather than an ovarian hypofunctionation. The best medicament for ovarian feeding at present, in our experience, is a glycerin extract of the entire fresh pig ovary.

Case. I. Mrs. R., aged 29, required in 1921 complete hysterectomy, with double oöphorectomy, for fibroids complicated by salpingitis with cystic and suppurative disease of the ovaries. On April 4, 1923, she presented herself with complaints of more or less constant and severe headache, very troublesome insomnia, marked constipation and the nervousness and frequent hot flushes of the artificially induced menopause. There had been no great gain in weight. She had been taking, without benefit, and in rather large dosage, 5 grain tablets of different ovarian preparations. Physical examination was negative. The pulse rate was 72; the systolic blood pressure, 115; metabolism and urine, normal. She was given the 10 minim pills of the glycerin extract of fresh pig ovary to take three or four times daily.

Ten days later, this patient professed to have been relieved of the

headache and much of the insomnia, but found that four of the glycerin extract of ovary pills produced anorexia and nausea. The dosage was then reduced to two or three pills daily. This seemed to improve the constipation. On June 9, 1923, all symptoms had disappeared and there were no complaints. There was no headache, no indigestion nor insomnia, and the bowels moved without the need of laxatives.

The headaches and insomnia began soon after hysterectomy and oöphorectomy, and had persisted in spite of the usual ovarian feeding until she had begun to take the glycerin extract of fresh pig ovary. After that was given the improvement had been rather gradual, but after two or three months all the abnormal symptoms had slowly disappeared.

At present, June, 1924, under this medicament the condition remains normal with an occasional slight headache, but more than ten to twenty minims daily of the glycerin ovarian extract has been found to induce nausea. In this case the symptoms were almost entirely subjective, but there can be little doubt of the marked improvement which could not be effected by any other means.

Case II. Mrs. C. H., aged 34, suffered from dysmenorrhea from the beginning of menstruation. When 19 she was "dilated" and curetted and wore a glass-stem pessary without relief. She married at 22 and became pregnant, but lost the child in a difficult labor followed by infection which required the removal of one tube and ovary. Two years later, a ruptured extra-uterine pregnancy with infection required another operation and the removal of the other tube and ovary. Following this, for the last five years there has been, of course, complete amenorrhea. With this there were the usual symptoms of the artificially induced menopause, but of considerable severity. For the past two or three years there has been noted a slight "goitre" (perceptible simple hypertrophy). The present complaints are those of weakness, coupled with a steady gain in weight; gaseous indigestion, constipation and troublesome insomnia. But more distressing than anything else, there is constant headache, chiefly in the temporal region. On physical examination, there were found the old laparotomy scars, a good color and a good general nutrition, but flabby musculature. There was a slight soft thyroid enlargement. The pulse rate was 76; systolic blood pressure, 250; weight, 146 lbs.; height, 5 ft. 6 in. Urine and blood examination were negative. She had taken "all kinds of treatment," especially different forms of ovarian feeding, but in spite of everything that had been done, the headache, blood pressure and gain in weight had steadily though slowly increased.

On February 6, 1923, she was given a 10 minim pill of the glycerin extract of fresh pig ovary to take four times daily.

On March 29, 1923, there was noted a marked improvement in the headache and strength, and some loss of flesh. The systolic blood pressure was 220, the weight 140. The 5% thyroid nucleoprotein tablets were then substituted for the glycerin extract of ovary.

On May 10, 1923, many of the former symptoms had returned, and the weight had increased to 150 lbs. The systolic blood pressure remained at 220. Glycerin extract of fresh pig ovary in 10 minim pills four times daily was then resumed.

On June 6, 1923, she reported that she had been freed of headaches soon after taking the ovarian pills. The systolic blood pressure had fallen to 170, and the weight to 148 lbs.

There were still some evidences of hyperthyroidism in the soft, slightly enlarged thyroid, the pallor, the weakness and defective gastrointestinal activity; consequently, she was given the 10 minim

pills of the glycerin extract of thyroid in conjunction with the glycerin extract of pig ovary.

On November 22, 1923, she reported that she felt very well, but any interruption of the ovarian feeding caused a recurrence of the headaches. If the thyroid was omitted there was defective energy and gaseous indigestion. The systolic blood pressure was then found to be 160 and the weight had decreased to 132 lbs. The thyroid enlargement had disappeared.

Since then she writes that the ovarian feeding has to be continued daily, but a little thyroid seems necessary to maintain her full strength and to prevent a tendency to become stout.

This case, though a little confused by the addition of thyroid to ovarian feeding, is clearly from the time of operation for the extra-uterine pregnancy, one of ovarian deficiency, and a less pronounced primary or former deficiency might be inferred from the dysmenorrhea which had existed from the outset of menstruation. Following the loss of the ovaries, there were the usual menopause symptoms and, in addition, the development of the headaches, the rising blood pressure and the increase in weight. That the blood pressure could be reduced by feeding glycerin extract of fresh pig ovary and not by any of the other ovarian products which had been given was quite evident. The coincident simple hypertrophy of the thyroid is suggestive of the thyroid-ovarian relationship; also, that the hypertrophy disappeared after thyroid and ovarian feeding. But the chief point is that the steadily rising blood pressure and alteration in general health was apparently stopped by ovarian feeding. That organ, in this particular instance, at any rate, might be called one that was essential for life. A blood pressure of 250 in a woman of 34 could not very long remain at that point without being followed by irreparable vasculo-cardio-renal disorders.

Case III. Miss D. W., aged 48, had the right lobe and isthmus of the thyroid removed in 1906 for hyperthyroidism. Complete recovery followed. In 1910 and 1914 there were mild signs of hypothyroidism, which were relieved by feeding thyroid nucleoprotein material. In July, 1923, she went to the country and the expected menstruation did not occur, and later the amenorrhea persisted. Very troublesome insomnia soon developed, and was accompanied by great nervous irritability and some mild delusions. She was then given by the local physician some tablets of corpus luteum and afterwards of desiccated whole ovary, but with negative results. The mental disturbance grew gradually worse, with pronounced hallucinations of sight and hearing. She was brought back to the city in September in a rather emaciated condition, and the disturbance then appeared to be a psychosis of the menopause with delusions of persecution. There was no other gross abnormality, except a slightly elevated blood pressure. The abdominal examination was negative, but on account of the four months of amenorrhea and mental condition no vaginal examination was attempted. She remained at her home under the care of a sister, and was given four times daily the 10 minim pills of glycerin extract of the pig ovary.

During the next three weeks the psychosis gradually grew less troublesome, and on October 11th menstruation appeared. After it had continued three weeks and was profuse, a vaginal examination revealed a fibroid uterus which could only with difficulty be palpated above the symphisis. As the menstrual flow was not excessive, and the psychosis was evidently improving, operation was deferred until the mental condition seemed normal. No peculiarities, except the bloody vaginal discharge, were noted after the middle of December, and on December 29, 1923, with considerable difficulty, the fibroid,

which was tightly wedged in the pelvis, was removed by supravaginal hysterectomy. Both ovaries were left in place. The left contained a corpus luteum. An uneventful convalescence followed, and as the psychosis had entirely disappeared, the glycerin extract of fresh pig ovary was discontinued. This patient was seen in June, 1924, and appeared perfectly normal.

The interesting points in this history are the amenorrhea and the following psychosis, neither of which was affected by the administration of the ordinary desiccated ovarian products. But after the administration of glycerin extract of fresh pig ovary the psychosis began to improve, and shortly afterwards the menstrual flow appeared. Its persistence led to the discovery of the hitherto unsuspected fibroid tumor of the uterus. The removal of the latter, after the mental condition had become normal, apparently because of the ovarian feeding, did not cause any recurrence of the psychosis.

Case IV. Miss E. B., aged 20, was first seen in February, 1921. She gave a history of dysmenorrhea accompanied by severe headache since the inception of menstruation at the age of 13. In 1916, the appendix was removed, but dysmenorrhea, especially on the right side, became worse. Early in 1919, the right tube and ovary were excised, apparently to relieve the pain. A few months later the left tube and ovary were removed to relieve the continued dysmenorrhea and "adhesions." Later the tonsils were excised. Following the double oöphorectomy constipation became excessive, and another laparotomy was performed for "adhesions," but without relief. After all these operations a slight "goitre" appeared and tachycardia became troublesome. In February, 1921, she presented the picture of typical, rather severe, exophthalmic goitre, but with obstinate constipation. The bowels could be moved only by prolonged daily irrigations.

Palliative treatment by iodin and adrenal feeding was tried for nearly a year, at first with some benefit, but later without gain.

In March, 1922, all four thyroid vessels were tied in two sittings under local anesthesia. Then the iodin and adrenal feeding produced a slow but steady improvement. In September, 1922, the Graves' disease seemed cured. The exophthalmos and goitre had disappeared; the pulse was 80, but the systolic blood pressure which was normal had risen to 145. The constipation was unchanged. "Hot flushes" and general nervous irritability were the other chief complaints. The glycerin extract of fresh pig ovary was then used for the first time.

In March, 1923, she reported that ovarian feeding relieved practically all of the distress except the constipation. She had lately been vigorously indulging in social pleasures, with dancing and late hours, and in April the tachycardia reappeared, and she needed treatment of the thyroid with x-ray. This, with rest, reduced the pulse rate to normal again in about one month. If feeding with the glycerin extract of fresh pig ovary was suspended, however, the "nervous irritability" and hot flushings returned. There was still very obstinate constipation, and the systolic blood pressure was 170.

In February, 1924, anorexia and nausea and then vomiting after each meal began. This gradually grew worse in spite of every kind of treatment, including rest in bed, sedatives, rectal feeding and gastric lavage. In June she was brought to the hospital again. The weight had decreased from 120 lbs. in February to 88 lbs. The pulse was 70; blood pressure, 140; there were no signs of thyroid disease; the urine was negative except for acetone. Fluoroscopic examination of the stomach (by Dr. A. L. Holland) was accomplished with some difficulty, but revealed no appreciable abnormality. The diagnosis

was nervous or hysterical vomiting. Nothing could be retained for more than a few minutes before entering the hospital. During the first three days there was a loss of weight of 2 lbs, and the acetone in the urine increased. Feeding by a duodenal tube was then instituted, and the glycerin extract of whole fresh pig ovary was added to the food; the vomiting promptly stopped. The tube was very irksome to the patient, and after four or five days first water, and then liquid foods were given by mouth, at first with the tube in place, and the vomiting did not recur.

This case is chiefly interesting because of the apparent causal relationship of the loss of the ovaries to the subsequent very serious developments. I have never before seen what seemed to be a pure hysteria threaten to come to a fatal ending. The patient through it all was calm (and in the hospital separated from sympathetic relatives), and evidently tried to help herself. Was the hyperirritability of the stomach really hysteria, or some neurosis of the stomach for which as yet there is no explanation?

This case has again relapsed and is again being treated with ovarian feeding and seems again improving.

CLINICAL SIGNIFICANCE OF THE CONGENITAL ABSENCE OF THE UPPER LATERAL INCISOR TEETH*

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Information is extremely limited concerning the significance of the congenital absence of the upper lateral incisor teeth. In spite of the limited information, opinions as to the causation and meaning of this condition are markedly divergent. Partly because of this lack of unanimity of opinion and partly because of the paucity of information, I have deemed the subject of sufficient general interest to warrant a presentation of the clinical findings of one patient in whom the upper lateral incisors are definitely deformed and three in whom the upper lateral incisors of the second dentition never appeared, and in whom radiographic examinations failed to reveal the presence of unerupted teeth.

PRESENTATION OF CASES

Case No. I. Sept. 17, 1924. Mrs. G. M., aged 27 years, white, attorney.

Complaints. Upper abdominal distress, lassitude, nervousness and chronic bronchorrhea were present.

Family history. The maternal grandmother, her oldest daughter, mother of the patient, and two youngest sons are subject to severe attacks of migraine. The patient's two sisters have very irregular teeth, although the upper lateral incisors are in position. Both the mother and maternal grandmother have been irregular in the menstrual periods. Two maternal uncles have suffered from nervous breakdown. One uncle recovered his health at the age of thirty years; the other has remained melancholic. He has four children, all of whom show marked dental anomalies.

Clinical history. The patient weighed 8½ pounds at birth. She was breast fed for a short time. There was considerable gastrointestinal trouble following the establishment of artificial feeding. On two occasions she had convulsions, which were considered the result of gastric disturbances. She was a fat baby and has always been overweight for her age and height. The present height of 60½ inches was attained at the age of 14 years.

Infantile eczema was an annoying condition during early life. She had measles when a child, and contracted mumps at the age of 14 years. Fever and chills (malaria) were common occurrences

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between the ages of 6 and 13 years—"I would go to school in the morning feeling fine, and be carried home in the afternoon with a fever."

The patient had a severe attack of sinusitis and many irrigations of the antrums about her 14th year. A second attack of sinusitis in 1921 was followed by an attack of severe vesicular dermatitis which ran a course of 14 weeks. A distressing catarrhal condition of the nose and throat and also persistent cough and bronchorrhea have been present since an attack of whooping cough at the age of 4 years. She has had two attacks of pleurisy without effusion. For these conditions she has had a great deal of local and general treatment, including the use of autogenous vaccines. At the age of 21 years she contracted pulmonary influenza, from which she "did not recover for months" and which left her respiratory tract "greatly weakened." She has been and continues to be sensitive to climatic changes and is prone to colds. The respiratory condition becomes much improved while in a dry, clear climate. The tonsils have been "removed on three occasions." She is subject to attacks of hay fever and asthma. Positive skin reactions have been obtained with cat hair and rose pollen antigens.

The skin has always been sensitive. Slight contusions cause marked discoloration, and irritation results in extensive "scaldings."

Menstruation was established at the age of 12 years and 3 months. The periods have never been regular. The time variation between periods has been from 2 months to 2 years. The menstrual flow, when established, usually lasts about 5 days and is not associated with headache, nausea or pelvic cramps. She was married at the age of 25 years but has never been pregnant.

The pulse for years has averaged around 60 per minute while quiet. Her normal temperature is 97.4 F. The basal metabolic rate a year ago was −9 per cent. She has received thyroid preparations with benefit.

She has led a rather active physical and social life. She is now engaged in the practice of law. She is very emotional, energetic and forceful. Only of late has weeping appeared in her emotional life.

Present status. For nearly a month she has noted an unnatural nervousness and just lately a diminution of the appetite—"an entirely new symptoms"—lassitude and a vague sense of depression. The loss of appetite has been associated with a vague, full, dragging distress in the upper abdominal region and slight nausea and aversion to food. The bowels are regular. There has been nocturia and frequent urination of late; however, urination has not been difficult or associated with distress of any sort. Her sleep is less sound and refreshing than formerly. She complains of being tired in the morning and again at about 3 p. m. "I feel hectic and all worn out." The emotions are less stable than formerly; she resents being alone. There are periods in which she experiences a sense of "internal emotions" which are not associated with tremors. These periods are usually followed by mild depression which is characterized by worry. There is a slight low backache. She has a persistent productive cough which is most marked in the morning. She does not complain of dizziness, night sweats, muscle cramps or joint pains. She has not menstruated for several months. Sexual desire is strong; however, there is delay in culminating the sexual act.

Physical examinations. The patient is of short stature and appears to be considerably over weight. There is marked fat padding

about the hips and over the shoulder girdle. The hands and feet are very small. The fingers are short and tapering.

Weight	68.6 K.	151 pounds
Height	152.5 cm.	60 inches
Torso	76.5 cm.	30⅛ inches
Lower	76.0 cm.	29⅞ inches
Span	142.0 cm.	55⅞ inches
Neck circumference	33.5 cm.	13¼ inches
Shoulder circumference	95.0 cm.	37½ inches
Axillary circumference	81.0 cm.	31⅞ inches
Abdominal circumference (at navel)	68.0 cm.	26⅞ inches
Trochanteric circumference	90.0 cm.	35½ inches
Head circumference (above ears)	54.0 cm.	21¼ inches
Head circumference (over vertex)	34.5 cm.	13⅝ inches
Interpupillary distance	5.8 cm.	2¼ inches

The skin is smooth, moist and cool. The hands and feet are cold to the touch. The head hair is abundant, coarse, very bushy and has a moderately high anterior attachment. The eyebrows and lashes are well formed; there is no nasal brow. The axillary and pubic hair is normal in amount and distribution. There is a growth of fine hair on the upper lip. The finger nails are smooth and brittle; the lunulae do not show.

The blood pressure is 112/64. The buccal temperature is 98.6 F. (usual normal, 97.4 F.). The pulse is 76 per minute (normal about 65), regular and of good quality. The heart sounds are regular. There are no cardiac murmurs. There is a cough which is productive of foul-smelling sputum. There are coarse bubbling rales over the midportions of the chest. Diaphragmatic movements are free and full. The vital capacity of the lungs is 2.6 liters.

There are small remnants of lymphoid tissue in the tonsillar fauces. The sinuses are clear upon transillumination. The mucosa of the nose and pharynx is quite reddened. The voice is rather low pitched. The tongue is clear and free from fissures or indentures. The palatal arch is moderately high. The dental ridge is quite wide. The upper central incisor teeth are very large and spaced (Fig. 1). The upper lateral incisor teeth are small and peg-like. There are numerous small white opaque spots in the teeth.

The basal metabolic rate is --2 per cent. The isthmus of the thyroid glands is not palpable.

Deep pressure over the upper abdominal region causes but little distress.

A gynecological examination made one year ago "was entirely negative." Vaginal smears show the presence of numerous pus cells, bacteria and epithelial cells.

The reflexes are all present and equal on the two sides. The knee jerks are very active.

Radiographic examinations. The heart and aorta are negative. The hilus shadows are considerably thickened and contain many calcareous areas. There is considerable generalized parenchymal infiltration radiating from the hilii. The apices and bases of the lungs are clear. Movements of the diaphragm are unobstructed.

The clinoid processes are large and nearly bridge over the sella. The floor of the sella is not definite in outline or position. The right mastoid cells are quite dense.

The bones of the hand and wrist are all present and of rather small size; the epiphyses are all closed.

Laboratory examinations. The Wassermann blood reaction is negative. The hemaglobin is 87 per cent (Dare). The blood counts show 2,944,000 erythrocytes and 20,900 leukocytes. A white count the following day showed 12,360 leukocytes. A third count was 12,120. The differential counts are as follows:

	9-18-24	9-19-24	10-20-24
Neutrophiles	63	66	65
Lymphocytes	7	16	3
Large mononuclears	27	14	29
Transitional cells	1	3	4

Figure 1. Photograph of dental impressions of the upper set of teeth in Case No. I. Note the large central incisors and the small, peg-like lateral incisors.

The urine has a specific gravity of 1020, an acid reaction and contains a faint trace of albumin. There are many bacteria and pus

cells in the voided specimen. Occasional pus cells are present in the catheterized specimen.

Diagnoses. The case is diagnosed as follows: present ailment, entero-pulmonic La Grippe or influenza; general diagnosis, hypofunction of the pituitary, thyroid and gonads.

Case No. II. Aug. 29, 1923. Miss N., aged 28 years, white, accountant.

Complaints. Convulsive seizures during the night, rapid increase in weight and urticaria during the fruit season were the outstanding symptoms.

Family history. See Fig. 2.

Clinical history. The patient has been continually over weight since birth. The deciduous teeth had to be extracted and the gums lanced to permit eruption of the permanent teeth. The right upper lateral incisor never appeared and repeated radiographic examinaitons have not shown an unerupted tooth. She contracted scarlet fever at the age of four years, from which she made an uneventful recovery. She was free from fits or convulsions as a child.

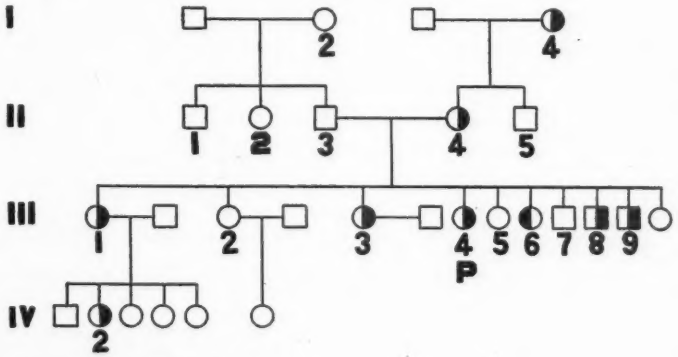

Figure 2. Genealogy of Case No. II.
I. 2. Died before the age of 30 years. 4. Congenital absence of the right upper lateral incisor tooth; no convulsions.
II. 1 and 2. Died of pulmonary tuberculosis. 3. Normal teeth; slender build; a large goiter. 4. Congenital absence of the right upper lateral incisor tooth; no convulsions.
III. 1. Congenital absence of the right upper lateral incisor tooth; no convulsions. 3. Congenital absence of the right upper lateral tooth; died following appendectomy. 4. Patient: Congenital absence of the right upper lateral incisor tooth; prognathism; nocturnal convulsions. 5. All teeth present; irregular menstruation; nervous; goiter. 6. Congenital absence of the left upper lateral incisor tooth; no convulsions. 8. Congenital absence of the right upper lateral incisor tooth. 9. Congenital absence of the right upper lateral incisor tooth; prognathism.
IV. 2. Congenital absence of the right upper lateral incisor tooth.

Bodily changes were not marked at the adolescent period. Menstruation was established at the age of fourteen years. The initial flow lasted five days. The periods occurred every twenty-eight days and were not associated with pelvic cramps, backache or headache. There was complete cessation of menstruation for a period of six months, following a fall into a river during a menstrual period, during her twenty-third year.

At the age of eighteen years the patient was thrown from a horse and sustained back and head injuries. She was unconscious for a few

minutes and bled freely from the nose. Two days were spent in bed and apparently she recovered completely from the accident.

The patient finished high school and took work at the university. She is now an accountant and successful in her work.

Present status. Four years ago the patient had a nocturnal convulsion which lasted but a few moments and which did not arouse her (convulsion witnessed by her mother). At that time her physician diagnosed her condition as the result of constipation. One year later she experienced a second convulsion and continued to have an attack each month for about six months. The last attack occurred in August, 1923, one year having intervened since the preceding attack. Convulsive seizures have never occurred during the day, or while awake. At no time have the seizures been associated with frothing at the mouth, loss of sphincter control or muscle soreness. The attacks are usually followed the next day by a severe frontal headache. On several occasions she has noticed dark spots in front of the eyes during the day preceding an attack. The patient thinks "that a full meal or extreme fatigue predisposes to an attack." The seizures have no relation to the menstrual period.

There is no stomach trouble. A considerable amount of fluid is taken each day. She craves and eats much starch and sugar. She suffers considerably with hives during the fruit season. The bowels are very inactive. For three years she has used cathartics daily—"I would go six days without a bowel movement if I did not take something." Throbbing frontal headaches occur as the result of constipation and are quickly relieved by a free bowel movement. She complains of bitemporal throbbing when she lies down. Glasses are worn. The menstrual periods are regular and free from distress. There has been a continual, steady gain in weight for the past three years—130 to 162 pounds. The fat is deposited mainly over the trunk and abdomen.

The patient is good-natured, keen to her surroundings and is "far from being temperamental."

Physical examination. There is marked fat padding, especially of the shoulders, upper arms, and about the hips. The breasts are pendulous and free from masses.

Weight	72.3 K.	159 pounds
Height	157.5 cm.	62¼ inches
Length of legs	84.0 cm.	33⅛ inches
Length of torso	73.5 cm.	29 inches
Spread of arms	166.5 cm.	65¾ inches
Circumference over shoulders	104.0 cm.	41 inches
Axillary circumference	95.0 cm.	37½ inches
Circumference of bust	105.0 cm.	41½ inches
Circumference at navel	90.0 cm.	35½ inches
Circumference over trochanters	110.0 cm.	43⅜ inches

The skin has an excellent color and is soft, moist and pliable. The hair of the head is abundant, lustrous, brown in color, of very fine texture and has a high anterior attachment. The eyebrows and lashes are well formed. Axillary and pubic hair is normal in amount and distribution. Hair is absent from the face and over the body save for a delicate growth on the forearms and legs. The nails are firm and smooth.

The tonsillar fauces are empty. The voice is clear and well modulated. The teeth are of moderate size, well spaced and of a clear bluish tint. The right upper lateral incisor tooth is absent. There are several devitalized teeth. The palatal arch is moderately high. The tongue is clear and free from markings.

Cervical glands are palpable along the left side of the neck. The

thyroid gland is not palpable. The basal metabolic rate is +1 per cent.

The heart, lungs, genitalia and rectum are negative. The reflexes are all present and equal on the two sides. Possibly the knee jerks are somewhat exaggerated. The blood pressure is 122/75. The pulse is 74 per minute and the temperature 98.2 F.

X-ray examinations. The heart is normal as to position, size and shape. There is no evidence of a persistent thymus gland. The diaphragm moves freely. The hilus shadows are moderately prominent.

The esophagus and stomach are negative. The duodenal cap fills evenly. Barium is retained at the inferior flexure of the duodenum. Reverse movements of barium in the duodenum occur frequently, although such movements are not associated with belching or nausea. This condition was most pronounced at a time when the colon was filled with barium from the preceding day's meal.

The cecum lies low and is not freely movable. The appendix was not visualized during the three days examination. The colon is especially spastic at the splenic flexure and throughout the descending portion. The colon and stomach are held well up in the abdomen. There are no points of tenderness or rigidity over the abdomen or pelvis.

Radiograms of the lateral head do not show changes about the sella turcica, although the sella is rather deep. The sinuses are of moderate size and clear. The epiphyses of the hand are closed.

Laboratory examinations. The Wassermann test is negative with cholesterinized antigen and the Noguchi modification, and positive 1+ to the ice box method with cholesterinized and Kolmer's antigens. The hemaglobin is 88 per cent (Dare). The red cell count is 5,456,000 and the white count 11,000 following the noon meal. The differential count shows neutrophiles, 53; small lymphocytes, 29; large lymphocytes, 13; eosinophiles, 2; transitional cells, 3.

The urine, on two occasions, showed faint traces of albumin.

Diagnosis. The patient has chronic appendicitis, allergy, hypophyseal obesity and petit mal (nocturnal) epilepsy.

Case No. III. May 18, 1923. Mr. F. E. S., aged 34 years, white, mechanic.

Complaints. There are pains about the heart upon taking a deep breath, shortness of breath, nervousness, cardiac distress when under moderate stress, backache for over four years which has incapacitated him for hard work, and night sweats for three weeks. He also complains of severe dizziness and frontal headache.

Family history. See Fig. 3.

Clinical history. The patient weighed 13½ pounds at birth. He was walking and talking at about twelve months. He was plump until the age of nine, at which time he began to grow rapidly in height. At the age of thirteen years he attained his present height. He now wears the same size shoe, hat and glove that he did at the age of thirteen years. At thirteen he wore a number thirty-six coat; he now wears a number forty.

He had mumps before the age of seven years. He had three attacks of measles, an attack of diphtheria, scarlet fever, typhoid-pneumonia at the age of nineteen years and pulmonary influenza at the age of thirty years. He has had blood poisoning on three occasions following local infections of the extremities.

At the age of eleven years he was kicked in the left parietal region of the head. The blow rendered him unconscious for a "considerable time" and was followed by immediate hemorrhages from the nose, ears, eyes and mouth. The nasal hemorrhage was not checked

until the third day. "I was bled white before they stopped the hemorrhage." Following this injury, the patient claims that he experienced daily hemorrhage from the nose—occasionally as many as thirteen a day—until the age of thirty-one years. Any sudden movement of the head, or moderate bodily strain was sufficient to incite a nasal hemorrhage. At the age of twenty-six years he was thrown from the roof of a street car, but managed to alight on his feet. There was no immediate disturbance following the fall; however,

Genealogy of Case No. III.

Paternal:

II. 1. Physician: 73 years old when first child was born to him by his first wife. Two sons and two daughters were born to him by his second wife, who married him at the age of 55 years.

III. 2. Male children either aborted or died in spasms immediately after birth. 3. Marked spacing of the upper teeth; height 5 feet, 11½ inches; weighed 140 pounds at 25 years of age and 280 pounds at the age of 57 years. Wife had congenital absence of the upper lateral incisor teeth. 4. Nurse; died of cancer of the stomach.

IV. 10. Wt. 8 pounds at birth; teeth markedly spaced; congenital absence of the left upper lateral incisor tooth. A daughter shows congenital absence of the left upper lateral incisor tooth. P. Patient: Wife has diabetes mellitus; she has conceived 5 times and brought only the first and last child to term; the other three were aborted before the 5th month of gestation. The first child was delivered at 8 months and lived 7 days; the fifth child was delivered two weeks over-time, weighed 12½ pounds and died within two weeks. 12. All teeth present; weighed 12 pounds at birth; drowned. 13. Drowned.

Maternal:

I. 1. Congenital absence of the upper lateral incisor teeth; husband's teeth "perfect."

II. 1. Died of Bright's disease at the age of 51 years; full set of teeth. 2. Congenital absence of the upper lateral incisor teeth; Bright's disease. 3. Congenital absence of the upper lateral incisor teeth; sugar in urine during latter part of life. 4. Congenital absence of the upper lateral incisor teeth; Bright's disease. 5. Teeth irregular and crowded; Bright's disease. 6. One of twins. Congenital absence of the upper lateral incisor teeth; operated upon at the age of 21 years for the removal of gall-stones; mentally unbalanced; kidney trouble. 7. One of twins. Died in spasms while very young. 8. Congenital absence of the right upper lateral incisor tooth. 9. "Teeth normal."

III. 1. Spacing of upper teeth. 10. Congenital absence of the left upper lateral incisor tooth. A daughter has a similar dental anomaly.

Wife:

I. 1. Died at the age of 96 years; sugar in the urine during latter years. 2. Second wife, living at 62 years of age; blind; sugar in the urine for several years.

II. 1. Died at the age of 39 years of diabetes mellitus. 8, 9 and 10. Died of diabetes mellitus.

III. 1. Died at 3 months from sun-stroke. 2. Eczema and diabetes mellitus; operation (1924) for congenital cystic endometritis. 3. Died in diabetic coma 1924. 4. Eczema; died at the age of 23 years of diabetes mellitus when 6 months pregnant. 5. Diabetes mellitus and an ovarian mass. 6. Eczema; died in infancy. 7. Diabetes mellitus; very nervous.

IV. 1. Menstruation at the age of 15 years; pulmonary tuberculosis during adolescent period. 2. Backward in school. 3. Died at 8 months because of "pressure on the spine." 4. Eczema and nervousness. 5. Nervous. 7. "Died of jaundice" at one week of age. 8. Lived 20 minutes. 9. Died at birth. 8 and 9 were "swollen blue babies." 10. Lived two weeks. 11, 12, 13. Miscarriages. 14. Died shortly after birth.

five days later he developed a severe backache which confined him to his bed for a week. Since the fall his back has remained weak and at times has incapacitated him for work. He states that his back has never been strong since the age of five years, at which time he jumped to the ground from a second-story window. There have been several light attacks of cystitis.

Adolescence appeared at the age of thirteen years; the voice changed and libido appeared. He states that since the age of thir-

teen he has been excessively passionate sexually and that he has over-indulged in venery ("Intercourse six to nine times in one night for as much as five nights running"). He denies having ever had a chancre or gonorrhea. He married at the age of twenty-five and was the father of five children, all of whom died either before, at, or soon after birth.

The patient finished the grade schools and spent two years at business college.

Since early youth, the patient has been subject to deep emotional depression and melancholia; however, he has never entertained the

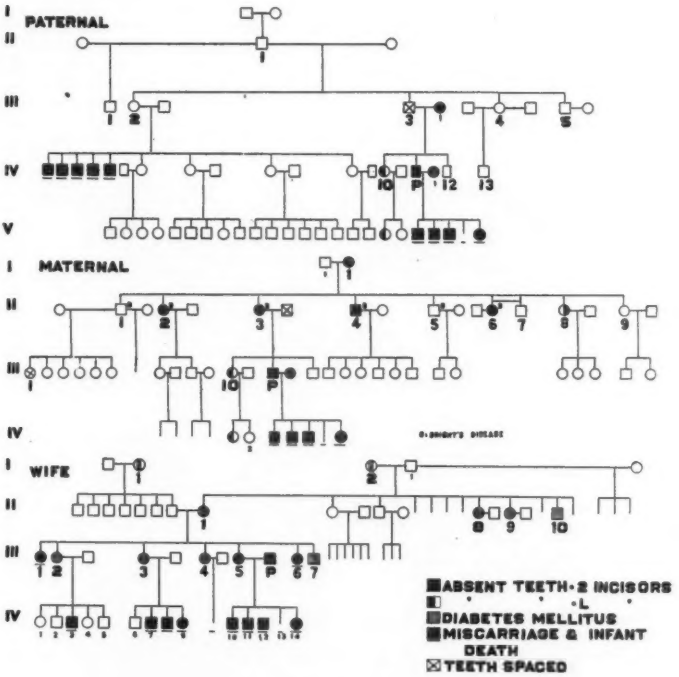

Figure 3

idea of suicide. He is not sociable, preferring to be alone and quiet. Excitement of any kind is distressing because it causes him to "flush and shake." He is quick tempered and subject to fits of anger in which he entirely loses self-control. "I go insane and blind and don't know what I am doing or saying." He states that his mother had a similar disposition. On three occasions he has nearly choked a man to death because of his unreasoning rage. Following such outbursts of emotion, he becomes remorseful and depressed. There has been no evidence of paranoia; however, he holds a grudge with considerable tenacity and forgives with difficulty.

Alcohol has been used in moderate amounts; tobacco excessively. He drinks from six to eight cups of coffee a day.

Present status. There has been a great deal of throbbing headache and dizziness for the last few months. There is a sense of extreme lassitude and physical inability. Moderate effort is followed by cardiac distress and dyspnea. There is a great deal of pain in the lumbar region and some in the neck. For several months he has been getting gradually more nervous and irritable. Libido has gradually become reduced.

Physical examination.

Height	168.0 cm.	66¼ inches
Weight	60.5 K.	133 pounds

There is a marked anemic pallor of the skin. The temperature is 98.0 F.; the pulse, 92; the blood pressure, 165/115. The tonsils are large and markedly infected. The urine is free from sugar, pus cells and casts; there is a faint trace of albumin. Radiograms of the teeth revealed the presence of four periapical abscesses; there is marked pyorrhea. The teeth are markedly spaced. The upper lateral incisors are absent and radiograms fail to show the presence of unerrupted teeth (Fig. 4).

Figure 4. Photograph of the dental apparatus of Case No. III. Note the marked spacing and absence of the upper lateral incisor teeth.

The patient was advised to have his teeth attended to and his tonsils removed. The teeth were extracted with marked improvement in his condition.

The patient returned September 9, 1924, complaining of tiredness and weakness in the morning and persistence of the backache. Since his previous visit there have occurred two persistent spots before the

left eye of which he is continually conscious. He has been free from dizziness for the past six months and headache for three months. The night sweats ceased soon after extraction of the teeth.

Second physical examination.

Weight	65.5 K.	144 pounds
Height	168.0 cm.	66¼ inches
Leg length	88.0 cm.	34¾ inches
Torso length	80.0 cm.	31⅝ inches
Span of arms	177.0 cm.	69¾ inches
Circumference over shoulders	108.0 cm.	42⅝ inches
Chest:		
Expiration	86.0 cm.	33⅞ inches
Inspiration	93.5 cm.	37 inches
Circumference at navel	81.0 cm.	32 inches
Circumference over trochanters	88.0 cm.	31⅝ inches
Circumference of head above ears	55.0 cm.	21¾ inches
Circumference of head over vertex	35.5 cm.	14 inches
Interpupillary distance	5.5 cm.	2¼ inches

The blood pressure is 190/98; the pulse, 90; and the buccal temperature, 98.8 F.

The skin is moist, has a normal color and "perspires freely." The head hair is straight, dark and has a moderately high anterior attachment. The eyebrows are well formed and there is no nasal brow. The axillary and pubic hair is abundant and of normal distribution. There is a moderate growth of hair over the chest, forearms and legs. The finger nails are hard and smooth. There is moderate acne over the back.

The tonsils contain a small amount of pus. The tongue is clear. Anterior cervical glands are just palpable on both sides of the neck. The sinuses are clear upon transillumination. The isthmus of the thyroid gland is barely palpable.

The chest is negative to auscultation, percussion and fluoroscopy. The diaphragm moves freely. There is definite left heart preponderance. The first aortic sound is slightly roughened and the second snappy.

The abdomen is negative to physical examination. The testes are firm. The right inguinal ring easily admits one finger. There are several small hemorrhoids which bleed easily. The prostate gland is of moderate size and not hard. There is some slight inflammation about the anus and over the perineum, puritus ani. The arches of the feet are quite high.

All reflexes are present and equal on the two sides. The knee jerks are very active. There is no Rombergism nor evidence of tremors.

There is some tenderness upon deep pressure over the upper lumbar spine. The curve of the spinal column is normal. The scapular borders show only moderate concavity.

Radiographic examinations. The lungs are clear save for a slight increase in the density of the hilus shadows. The domes of the diaphragm are smooth; diaphragmatic movements are normal. There is moderate hypertrophy of the left ventricle. The mediastinum is negative.

The plate of the lateral head shows the skull to be of uneven thickness. The occipital protuberance is very prominent. The sella turcica is large. The clinoid processes are prominent. The mastoid cells are extensive and clear.

The osseous structures of the pelvis are normal. The sacral joint does not show pathological changes.

Laboratory examinations. The urine has a specific gravity of 1006 and an acid reaction. Occasional pus cells and a faint trace of

albumin are present in the urine. The kidney function test shows a 50 per cent return of the dye in two hours and fifteen minutes. There was a total secretion of urine of 1020 cc. during the test period. The cystoscopic examination is entirely negative.

The Wassermann reaction is negative. The hemoglobin is 101 per cent (Dare). Cell counts show: 5,568,000 erythrocytes; 8500 white cells. The differential count shows: neutrophiles 71; lymphocytes 7; large mononuclears 21; and eosinophiles 1.

Diagnoses. The case is diagnosed as follows: present ailment hypertension and mild tonsilitis; general diagnosis, anterior lobe hyperpituitarism.

Case No. IV. Aug. 13, 1923. Miss F. S., age 15 years, white, student.

Complaints. There is a constant productive cough, profuse expectoration and malnutrition.

Family history. The mother has been operated upon for cancer of the breast and a ruptured appendix. She is of short stature and slight build; her two sisters are "above the average height." The father is living and has a marked anemic pallor. He was short and very fat until his seventeenth year, following which he "shot up all at once and became quite thin." The one sister is feeble-minded and is a typical case of dystrophy adiposogenitalis. The mother, sister, father and two maternal aunts have normal upper later incisor teeth.

Clinical history. The patient weighed ten pounds at birth and continued over weight until the age of two years. She was speaking a few words at twelve months. She suffered a severe attack of thrush during her second year; this lasted three months. Ten of the deciduous teeth were lost during this attack of thrush. She has had measles, chicken-pox and pulmonary influenza. At 11 years of age she contracted whooping-cough, from which time there has been present pulmonary distress, cough and profuse expectoration. She is subject to colds.

The permanent teeth were slow in erupting and were irregularly spaced. The upper lateral incisor teeth have never appeared. Glasses have been worn since the age of seven years because of diminished vision, myopia and right eye squint. Growth was slow and continued until her fourteenth year.

Menstruation was established late in her fifteenth year. The initial flow lasted nine days. Nausea and back pains were experienced the day preceding the flow.

She finished grammar school at the age of fifteen years.

Present status. The appetite is good and the bowels are regular. Sleep is sound and refreshing. There is no nocturia or distress upon urination. There is a deep, harsh cough which is productive of large quantities of foul-smelling muco-purulent matter.

There is no complaint of headache, dizziness, nausea, muscle or joint pains, lassitude or emotionalism. She is energetic, sociable and serious minded.

Physical examinations. The patient is under-nourished, of small stature and poor posture. The shoulders are stooped and the sternum sunken.

Weight	42.7 K.	94	pounds
Height	154.5 cm.	61	inches
Torso	77.5 cm.	30½	inches
Lower	77.0 cm.	30¾	inches
Spread of arms	156.0 cm.	61⅝	inches
Circumference over shoulders	88.7 cm.	35	inches
Circumference at umbilicus	65.0 cm.	25⅝	inches
Circumference over trochanters	80.0 cm.	31⅝	inches

The skin is rough and mottled. The hands and feet are livid and cold to the touch. The cheeks are markedly flushed. There are numerous small moles over the right side of the face. The head hair is fairly abundant, of fine texture and has a high anterior attachment. The eyebrows and lashes are well formed. Axillary and pubic hair is abundant and of normal distribution.

The cheekbones are prominent (American Indian type). The joints are large and pliable. The breasts are well developed.

The palatal arch is low and the dental ridge fairly wide. The teeth are irregularly placed. The upper central incisor teeth are markedly spaced and show transverse striations near the gums. The upper lateral incisors are absent (Fig. 5). The first upper premolars of the second dentition have been extracted. The lower central teeth are crowded and show longitudinal ridging. All of the teeth have a dirty yellow color which is most marked near the gumline.

The thyroid gland is moderately and uniformly enlarged—simple goiter.

The blood pressure is 105/55; the pulse, 74; the buccal temperature, 97.4 F. The heart is negative as to murmurs. There are

Figure 5. Photograph of the teeth of Case No. IV.

numerous coarse rales throughout the right upper chest. There is definite tympanites over the right upper chest.

The reflexes are all present, active and equal. The knee jerks are very active. There is no clonus, tremor or Rombergism.

Radiographic examinations. The heart and mediastinum are negative. There is considerable inflammatory reaction in the hilus regions associated with peripheral radiation. The condition is most marked in the right chest.

A radiogram of the lateral head shows almost complete osseous bridging of the sella turcica. The sphenoid sinus is quite large. The epiphyses of the wrist and hand bones are open.

Laboratory examinations. Sputum examinations were repeatedly negative for the tubercle bacillus; the urine is negative for sugar, albumin, pus cells and casts.

Diagnosis. The following diagnoses are made: present ailment chronic bronchitis; general, goiter (simple), myasthenia and faulty nutrition.

REVIEW OF LITERATURE

A dental surgeon, R. C. Lucas, in 1888 published data concerning several patients in whom an upper lateral incisor tooth

was absent, or if present, deformed and very small (1). These patients had children with congenital deformities, in most cases harelip and cleft palate. The only man in the series had an only child, a daughter, who, like her father, had no upper lateral incisor tooth. This author, from his observations concluded that "the absence of a lateral upper incisor tooth resulting from an arrest of development is to be regarded as a malformation closely related to harelip and cleft palate, and is capable of transmitting each or both of these deformities to a succeeding generation."

In a second paper, which appeared in 1904, Lucas states "that some dental surgeons present" at the presentation of his first paper "declared that lack of eruption of certain teeth of the second set was a matter of common observation, and that no clinical importance need be attached to it." However, the author still contended that such defective dental development is a danger signal as to results that might follow in succeeding generations.

The work of Lucas, aside from creating an immediate school of opposition, made little impression upon the medical and dental world, for the subject appears not to have been considered again until twenty-nine years later, when Kaplan, 1917, without presenting evidence, associated deformity and absence of the upper lateral incisors with the internal secretion of the gonads.

Kaplan (2), apparently unaware of the papers by Lucas, deals with the subject of the incisor teeth as follows:

"If the middle upper incisors carry a message from the pituitary, the lateral upper incisors certainly do the same from the gonads. So that when the gonads are teratologically ab ova, definitely abnormal, one is sure to find some abnormality in the upper lateral incisors. The relationship, if any, is a crossed one, so that the right upper lateral incisors may point to the left testis or ovary, and vice versa."

"It is also to be noted that the greater the deviations from normal, the more definite the markings in the dental department, so much so that the lateral incisors, as a result of marked gonad defect, may not have erupted at all. Such a dental situation is rare indeed, so is also the clinical condition presented by the patient who has it."

"In the male, small and stumpy laterals bespeak sexual impotence on the physical basis."

The year following the appearance of Kaplan's paper, Timme, 1918 (3), in discussing "a new pluriglandular compensatory syndrome," refers to the dental apparatus as follows:

"The teeth are usually delayed in their appearance. They also show certain characteristics. The lateral incisors, especially in girls, are frequently underdeveloped. The canines, likewise, are either underdeveloped or else take on the flat appearance of incisors, losing their fan-like appearance."

An extensive search of the literature has been unproductive of further information save the incidental statement of Mebane (4). This author, in discussing "the teeth in childhood," states that "congenital absence of any permanent teeth may occur" and that "absence of one or both upper lateral incisors is the most common." Aside from this statement the subject is not discussed except to state that extraction of the tooth opposite the absent one is one of the few instances in which extraction is justified in the treatment of malocclusion.

DISCUSSION

Consideration of the subject of malformation or congenital absence of the upper lateral incisor teeth, as previously noted, has given rise to three distinct schools of thought. In brief, the contentions of the three schools are as follows: (1) Lucas believes the condition to be an indication of the appearance of transmissible developmental malformations; (2) Kaplan asserts that the anomaly is the result of a gonadal deficiency; and (3) Timme states that it is indicative of a pluriglandular compensatory syndrome. To these should be added a fourth school. This latter school, although not recorded in the literature, as far as I have been able to ascertain, while recognizing the facts, contends that such have no clinical significance aside from that of human curiosity conditioned by the presence of the unusual.

It would appear that factors other than those already mentioned should be thoroughly considered before there will be forthcoming a feasible theory to explain the causation and meaning of developmental anomalies of the upper lateral incisor teeth. The question of the influence of periapical abscesses of the deciduous teeth upon the buds of the permanent set, the question of the elimination of unnecessary bodily members by processes of evolution and influences of environment, and, also, the question

of the hereditary nature of transmission of congenital defects and developmental arrests must be considered as possible factors in the production of dental anomalies before the dictum of either Lucas, Kaplan or Timme can be accepted without reserve. Investigation along such lines, of necessity, are laborious; however, ease should not prejudice to the extent of permitting one to deny any significance of so definite a phenomenon as the congenital absence of a tooth, especially if such is found to be a transmissible character.

HEREDITY AND THE UPPER LATERAL INCISORS

If the contentions of Lucas are correct, then the problem of the congenital absence of the upper lateral incisor teeth is reduced to a consideration of teratogenic factors: a study of progeny generally, and teratogeny specifically.

It is not feasible at this time to deal extensively with the problems of heredity; however, the genealogies of the patients whose case histories have been presented are of sufficient interest to warrant comment.

The mother and two sisters of the first patient have very small, peg-like upper lateral and massive central incisor teeth. The deformity of the incisors is more pronounced in the three sisters than in the mother. According to tradition, the maternal grandmother had the normal number of teeth, the upper lateral incisors showing slight torsion but of usual size. In this instance it appears that the dental anomaly was transmitted through the female line and that it has become more marked in each successive generation. Because of this fact one wonders if succeeding generations will have members showing congenital absence of the present deformed teeth.

The genealogy of the second patient is of interest in that a congenital absence of the right upper lateral incisor has appeared in four successive generations. As shown in Fig. 2, transmission of the dental anomaly has occurred only through the female line. Another point of interest in this genealogy is that of the ten children (seven girls and three boys) born to the patient's mother, four girls and two boys, a total of six children, are minus an upper right lateral incisor, save one girl who is deficient in the left lateral incisor. Because of this latter fact the question is raised as to the probability of bilateral absence of

the upper lateral incisors in members of succeeding generations.

Special interest is attached to the family history of the third patient because of the array of dental anomalies. The maternal grandmother, who lacked the upper lateral incisors, gave birth to nine children, including twins of opposite sex. Of the five girls, three had a dental condition similar to that of the mother and one had an absence of the right upper lateral incisor. One of the boys had teeth like his mother. The boy twin died young; the other two boys had the normal number of teeth. The third child, a girl, who had congenital absence of the upper lateral incisors, gave birth to a girl and two boys. The girl had congenital absence of the left upper lateral incisor. She married and has two daughters, one of whom has a dental anomaly similar to that of her mother.

The point of interest here is the partial recovery from the dental anomaly in the third and fourth generation; a condition quite the opposite that of the first patient. One brother, the patient, had absence of the upper lateral incisor the same as his mother and maternal grandmother. He married a woman who came from a line of diabetics, and herself has diabetes mellitus. She became pregnant five times, but none of the children lived longer than a few days after birth. Because of this, nothing can be said concerning the possibility of transmission of the dental defect through the paternal line. However, an uncle of the patient, who had congenital absence of the upper lateral incisor, married and had three boys and three girls, all of whom have the normal number of teeth.

It is unfortunate that the pair of twins in this family did not live to maturity, inasmuch as the girl, who survived to adulthood, has congenital absence of a lateral incisor, as did her mother. Had the boy grown to maturity and possessed the normal number of teeth, we should then have had a condition somewhat analogous to that of mongolianism appearing in one of two-sexed twins. Such a condition would of necessity demand a close differentiation between hereditary and congenital factors in the production of such variations in twins.

The fourth patient, though showing marked deformities in the dental apparatus, is free from any known hereditary factor to account for her condition.

Congenital anomalies other than those shown in the dental

sphere have not occurred in the genealogies of the four patients presented. Further, in a series of 16 cases of congenital absence of upper lateral incisor teeth, the family histories of whom are available, there has not appeared a single known instance of harelip or cleft palate. The only instance of malformation was that shown by a maternal uncle who was born without arms. These observations are quite different from those collected by Lucas; however, the present genealogical findings in no way vitiate those of previous observers. The collected facts remain as observed; the theories evolved for explanation of the facts, of necessity, are based upon considerations of available data.

FERTILITY AND THE UPPER LATERAL INCISORS

The statement of Kaplan, "when the gonads are teratologically ab ova definitely abnormal, one is sure to find some abnormality in the upper lateral incisors," offers little solace. Moreover, the statement appears ambiguous in that one is permitted to assume either that the dental anomalies are conditioned by monstrosity of the ovum, that is, of the germ plasm, or by deficiency of the postulated internal secretion of tissues anatomically associated with germ cells. The use of the collective term gonad is always confusing in that one is forced to interpret its meaning, and such interpretations often give rise to much misunderstanding.

If Kaplan means that teratological conditions in the germ tissue are responsible for dental anomalies, then his explanation of the phenomenon is similar to that of Lucas, namely, the appearance of a transmissible anomaly. On the other hand, if he means that the appearance of dental anomalies is the result of the gonads, then one is forced to conclude that the anomaly is either the result of a congenital (accidental) defective endocrine principle or that the endocrine deficiency is the factor transmitted. Acceptance of the latter conclusion in no way simplifies the explanation of the conditions "teratologically ab ova" which cause the dental anomaly. In fact, such a conclusion merely shifts the transmissibility of dental anomalies from dental anomalies, as such, to that of an endocrine principle which, because of its presence, permits the dental anomaly to appear.

From the nature of Kaplan's statements I assume that he

is dealing with the relation of the internal secretions of the gonads to the upper lateral incisors. In any event, it appears that much evidence must be compiled before such a relationship can be accepted with safety. Moreover, there should be complete differentiation between reproductive (germ plasm) and bodily (somatoplasm) functions when speaking of the gonads.

The contention of Kaplan, also that of Timme, would seem vindicated in the light of the findings of my first patient. However, if this patient is to be classified as belonging to the pluriglandular syndromes, then not she alone but also her mother and maternal grandmother must be similarly classified, for each was small of stature—sixty-two inches—and each was subject to marked irregularity of menstruation. It appears, however, that the patient's maternal ancestry were far from being sexually impotent or unproductive; the grandmother gave birth to five boys and one girl, and the mother to three girls and a boy, and there were two miscarriages.

There is no evidence of sterility in the mothers of the second and third patients. For instance, the mother of the second patient, who lacked the right upper lateral incisor tooth, a condition similar to that of her mother, gave birth to ten children (seven girls and three boys), six of whom never developed a lateral incisor. The oldest child, a girl, with dentition like that of her mother, married and give birth to four girls and a boy. The oldest daughter, like her mother, grandmother and great-grandmother, is minus a right upper lateral incisor.

The grandmother of the third patient, whose dental anomaly consisted of absence of both upper lateral incisors, gave birth to nine children, including a pair of twins. Three of the girls and one boy had dental characteristics similar to those of the mother, and one girl was deficient the right upper lateral incisor. Eight of the nine have married, and seven have families; a total of twenty-four offspring.

The factors responsible for the establishment of sexual maturity appear to have been normal in the cases reported. Menstruation was established in the first patient at twelve years and three months; however, the menstrual periods have never been regular. In the second patient, maturity occurred at the age of fourteen years. In her case menstruation has continued regular save for a period of about six months following an acci-

dent. Menstruation, in the fourth patient, did not appear until the age of fifteen years. Sexual maturity occurred in the third patient at the age of thirteen years. Libido and potentia are considered normal or possibly slightly accentuated in the first patient. The third patient asserts that libido has been marked since the age of thirteen years and that venery has been excessive. Just the opposite condition was found to exist in another patient, a man, who has congenital absence of the right upper incisor tooth.

Conclusions relative to the fertility of persons possessing congenital anomalies of the upper lateral incisors must wait upon more extensive data than are now available.

INTERNAL SECRETIONS AND THE UPPER LATERAL INCISORS

I do not wish to discuss at length or intend to draw conclusions relative to the possible endocrine significance of anomalies of the upper lateral incisors. I do, however, wish to present the endocrine aspect of the four patients, the case histories of whom have been given.

The clinical findings of the first patient are such as to indicate a rather marked dyspituitarism. This assumption is derived from the fact that the torso length is less than that of the lower portion of the body and the span greater than the height. To these may be added the small, nearly bridged sella turcica, the small sinuses, the small hands and feet with tapering phalanges, the terminal digits which are free from tuberosities or tuftings, the broad pelvis and genu valgum. The slow pulse, low temperature and blood pressure, the high carbohydrate tolerance, the girdle, mons and mammary adiposity, intestinal atony, freedom from uterine cramps and periods of apathy, may also be taken as evidence of a functionally feeble pituitary gland.

According to the teachings of Falta (5), an osseous development as shown by the patient (the distance from the symphysis to the heel greater than from the symphysis to the top of the head) is diagnostic of primary genital dystrophy. However, sexual maturity (menstruation, libido, potentia and secondary sex characters) appeared early in this patient, and with their appearance growth ceased. In spite of the early appearance of sex maturity, there has continued a marked degree of amenorrhea and there is, at the present time, a definite growth

of hair on the upper lip. These gonadal symptoms, according to Engelbach (6), may be explained upon an assumption of post-adolescent hypoantuitarism.

Disturbed endocrine function is further evidenced by the depressed basal metabolic rate. This, together with the fact that thyroid medication resulted in a marked improvement of the general health, is indicative of an under-functioning thyroid gland. Certain other symptoms are readily explainable by assuming a weakened function of the suprarenal bodies, but of this, enough. In concluding this case we may diagnose as follows: (1) primary genital dystrophy; (2) postadolescent hypoantuitarism associated with thyroidal and gonadal insufficiency; or (3) pluriglandular syndrome. Truly, in this patient Kaplan finds vindication for his gonadal theory of incisor anomalies; Timme of the pluriglandular theory, and Lucas for that part of his theory which contends for the transmissibility of such characters.

The general osseous development of the second patient is quite similar to that of the first. The leg length is 10.5 cm. greater than that of the torso, the span is 9 cm. greater than the height, and the hands are small and tapering. The sella turcica, however, is roomy, and the sinuses are of average size.

The increased carbohydrate tolerance, the typical moderate girdle, mons and mammary adiposity, epileptiform seizures, intestinal inactivity and absence of uterine cramps, may be looked upon as evidence of hypophyseal deficiency. In opposition to this assumption is the absence of apathy, a normal basal metabolic rate and the menstrual disturbances so frequently associated with anterior lobe disorders (Engelbach). However, the present type of adiposity rather definitely incriminates the pituitary organ as responsible for her present status and an early primary genital dystrophy for her osseous development.

The third patient must be considered as showing initial endocrine disturbances if we follow the dictum of Engelbach relative to birth weights, for he weighed 13½ pounds when delivered. Overweight was continued until the ninth year, at which time he "thinned out" and grew rapidly until the establishment of sexual maturity at the age of 13 years. This growth period may be looked upon, as suggested by Engelbach, as one of active function of the pituitary gland. Continuance of an active pitu-

itary function is evidenced by the large and separated upper incisors and a definite degree of spacing of the lower teeth. The peculiar bodily proportions (torso greater than lower length and span greater than height) and mild prognathism, also may be looked upon as pituitary characters.

Inhibition of growth (height) occurred in this patient, simultaneously with the appearance of sexual maturity. Sex instincts and functions, since their appearance, have been excessive. This condition may be looked upon as the result of either "hyperfunction" of the gonads primarily, or secondarily as the result of pituitary stimulation. In either instance the situation is quite opposite to that observed in the first two patients. Indeed, we may look upon this patient as giving evidence of very active gonadal and pituitary functions.

The acceptance of such a conclusion, of necessity, raises a difficulty in the acceptance of a theory of gonadal deficiency to explain the absence of the upper lateral incisor teeth unless one wishes to argue that gonadal functions, weak by nature, have been excited to excesses by reason of an unchecked pituitary gland.

The fourth patient, like the third, was overweight at birth and continued so until the attack of thrush during her second year. Growth was slow and menstruation did not appear until the fifteenth year. In spite of the family history, which is highly suggestive of pituitary dysfunction (an only sister with primary dystrophy adiposa genitalis, a very short mother, and a tall father), the patient's measurements are normal, i. e., the torso and lower measurements are equal. Aside from the information relative to the birth weight, measurements and date of onset of menstruation, but little is to be said relative to the endocrine system. The long continued series of infections have so occupied the clinical field that present conditions are not justifiably to be considered alone the result of endocrine factors. Indeed, it may be that the present dental anomalies are explainable on the basis of an infectious process.

Before leaving the subject of the gonads I wish to call attention to the dental apparatus observed in a case of pseudohermaphroditism. The patient, who was twenty years of age, consulted her family physician because of the non-appearance of menstruation and sex instincts. Examination revealed a penile

organ about two inches long, with a well developed glans and prepuce and an indenture indicating the meatus (Fig. 6). The urethra, however, opened directly beneath the penile organ. A second opening, the vaginal inlet, barely admitted a probe. The breasts were undeveloped and appeared like those of a male. The

Figure 6. Photograph of the external genitalia of a case of hermaphroditism.

voice was heavy, the features coarse, and there was a definite growth of hair on the chin and upper lip.

Because of chronic trouble of the appendix and a possible marriage the patient underwent an operation for appendictis and amputation of the penile organs. At operation the internal

genital organs were found to consist of what appeared to be a minute uterus from which a small tubular structure passed laterally on either side to a mass of greatly vascularized tissue about the size of the end of the little finger. Removal and section of one of these masses showed it to be composed of blood vessels and tissue in which no evidence of gonadal cells of either sex could be demonstrated.

The patient had a wide dental ridge and a high palatal arch. The teeth were large, well spaced, in excellent alignment, of good color and free from spots or ridges. The upper lateral incisor teeth were well formed and in good position.

The findings on this patient are of special interest in that a marked gonadal and sexual malformation exists in the presence of an excellent set of teeth in which the upper lateral incisors are present, well formed and in normal position.

Such findings frankly belittle the conclusions that too easily might be drawn in relation to gonadal deficiency in persons with anomalies of the upper lateral incisor teeth. One is forced to continuous evaluation of information in the presence of such apparently contradictory findings. Collected observations of the dental apparatus in hermaphrodites, both false and true, would undoubtedly furnish weighty evidence for or against the theory of a "gonadal deficiency" as a causative factor in the production of dental anomalies.

POSTNATAL FACTORS AND THE UPPER LATERAL INCISORS

The clinical history of the fourth patient in this report was presented primarily to raise the question of postnatal factors in the causation of the nonappearance of the upper lateral incisors. This patient contracted a severe attack of thrush from which she nearly died, and as a direct result of this infection lost ten deciduous teeth. Completion of the second dentition occurred without the appearance of the upper lateral incisors. Inasmuch as the patient is free from any apparent hereditary cause to account for the absence of the incisors, there is the possibility that the attack of thrush not alone caused her to lose ten of the deciduous teeth but also caused destruction of the buds of the second dentition. If such is the proper explanation, it is strange that the upper lateral incisors alone should have suffered the insult.

Irrespective of the present case, it appears, inasmuch as

destructive processes are known to cause irregularities in the architecture of the teeth (for instance the dental markings associated with parathyroid deficiency), that destructive agencies might cause decalcification and absorption of tooth buds. It is conceivable that an abscess at the root of a deciduous tooth might work complete destruction of the undeveloped tooth beneath. Definite information concerning such an assumption to account for absent teeth will most easily come from the dental profession. However, such information will be of value only after the possibility of hereditary causes has been eliminated and a definite history of sufficient causes to produce such an absence obtained.

EVOLUTION AND THE UPPER LATERAL INCISORS

Any statement relative to the evolutionary significance of the subject under discussion is decidedly hazardous at the present time. However, it appears, inasmuch as the upper lateral incisor teeth are the ones most commonly observed to be deficient or absent, that a factor of selective elimination is manifest in the human race. Orthodontists, with whom this subject has been discussed, are inclined to look upon it as an evolutionary factor substantiating their opinion by pointing to the upper lateral incisors as the least useful ones in the dental arch.

CONCLUSION

Apparently congenital defects of the upper lateral incisor teeth are rather common. During a period of three years I have succeeded in collecting 20 cases of congenital absence of the upper lateral incisor teeth. Partial systematization of the data on these 20 cases has not been suggestive of explanations other than those given throughout the course of this paper.

The foregoing presentation has been offered primarily to state the possible theories that may be put forward to explain the etiology of the absence of lateral incisors. The four cases presented offer many possibilities for theorizing; however, it appears to me that specific data on this subject are not available in a number that would justify an attempted conclusion regarding the problem.

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CASE OF PLURIGLANDULAR DYSCRASIA

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The case described below is interesting for several reasons. It first appeared as a case of obesity and achondroplasia. Only close examination of the history, of the physical findings, and finally the x-ray plates, made it necessary to rule out this condition and seek for another clinical diagnosis.

Krabbe lately drew attention to the fact that cases of precocious puberty frequently simulate achondroplasia. He introduced for these cases the name pseudo-achondroplasia. Precocious puberty was also a prominent but not sole feature of our case. Further examination indicated that a number of the endocrine glands were involved. As in most such cases, the symptoms were not those of mere hyper- or hypo-function, but in the same gland there seemed to be partial functions exaggerated, while others were attenuated, thus presenting a picture of real dyscrasia.

Case No. 1759. Miss H. S., Hebrew, age 18 years, school-girl.

Family history on the father's side was negative. On the mother's side all the family are stout. One of the patient's aunts developed mild diabetes in her twenties and on slightly restricted diet has been sugar-free for a number of years.

A cousin of the patient developed dyspneic attacks at the age of eight months. Roentgen ray examination showed an enlarged thymus. On x-ray treatment (two or three sessions) the condition cleared entirely.

Past history. The patient was delivered at term by forceps, with slight trauma to the forehead, which cleared in a week.

Her weight at birth was 7 or 8 lbs. She was a fully developed and very stout baby and weighed 33 lbs. at the age of one year.

At the age of four she had very mild scarlet fever, with complete recovery in six weeks without complications or sequels. She had measles at the age of seven years, and chicken-pox at eleven, both very mild, without complications. Chorea (?) at the age of 8-9 years lasted for a few weeks.

She started to talk at the age of six months and was able to talk fluently at one year. At the age of 18 months she spoke like a child of four years. Teeth came at the normal time. She started to walk at the age of 17 months.

She was able to read at the age of 5 years. In school she was always one of the best pupils, mentally very bright. Myopia was discovered at the age of 6-7 years.

At the age of 8-9 her breasts began to develop and grew unusually large. Two years later she started to menstruate. The first period lasted for about a week, the next did not come for two months, and since then she has menstruated regularly every four weeks. The second menstruation lasted about two weeks, the subsequent ones about 6-7 days with moderate discharge and slight pain.

The axillary and pubic hair developed at the age of 11 years. At the same time the hair of her head became coarse and dry. Her growth at this time was very slow and stopped entirely at 13 years.

She first became obese at the age of 5 months. A second increase of obesity occurred at the age of 9 years, at the same time as her breasts developed.

She is mentally very active and a great reader. She refused, as a child, to play with other children, because "they were stupid." Now she does not make any friends. She talks much, is extremely moody and has a disagreeable disposition. She feels sometimes very old ("190 years").

Physical examination. The height is 146 cm.; plantar-symphseal measurement, 58 cm.; plantar-umbilical distance, 74 cm.; distantia spinarum, 28 cm.; distantia cristarum, 24 cm.; distantia trochanterica, 30 cm.; humerus, 31 cm.; forearm, 21½ cm.; femur, 30½ cm.; leg, 30½ cm. The skull measurements were lost, but the circumference is unusually large. The weight is 160 lbs. There are fat pads over the shoulders, the lower part of the abdomen, buttocks and thighs. There is comparatively little fat on the thorax and limbs. The skin is smooth and tense, not dry. The hair is very thick and coarse. Axillary and pubic hair is scanty. There is a slight mustache.

The mammae are about 35 cm., nearly free of fat; on palpation they seem to consist of lobulated adenomas. At places there is slight tenderness; a few adenomatous nodes can be distinctly separated from the surrounding tissues, varying in size from a walnut to an orange.

The pupils are equal, and react well to light and accommodation. The reflexes are normal. The thyroid is not palpable. A few lymph nodes in the axilla are palpable. The teeth are intact. The tonsils are somewhat enlarged. The lungs are normal. The heart is small; the sounds are well defined, and there are no murmurs. The pulse is regular; the rate at rest is 82, after exertion 98, and it returns within 1½ minutes to the former rate. In the abdomen there are no masses; slight tenderness is felt over MacBurney's point. No examination of the genital organs was made.

The red cell count was 5,500,000; leucocytes, 9800; polymorphonuclears, 61%; lymphocytes, 32%; eosinophiles, 4%; basophiles, ½%; monocytes, 2½%; hemoglobin (Tallquist), 90%. The blood sample was taken 3 hours after breakfast.

Eye examination gave the following results: O.D.9.200, —3.50 axis 30, 15/40 two letters; O.S. —1.25— —3.00 axis 150, 150/30 two letters. The muscle test shows an exophoria of 3° for distant vision and a left hyperphoria of 1°. The ophthalmoscopic examination shows negative fundus. The examination of her fields of vision by the perimeter shows the field for form to be approximately normal. In the right eye there is a cutting off above of about 15°. The field for blue is quite contracted in both eyes (more in the left), and the field for both red and green is contracted. Examination did not confirm any pressure from the pituitary gland or nasal sinuses upon the optic nerve. (Dr. Calvin Williams, New York.)

Basal metabolism tests were as follows: January 31,—20% (before thyroid treatment); February 23, +11% (5 grs. of thyroid twice

daily); March 29, —3% (thyroid stopped). (Dr. Benjamin Jablons, New York.)

Laboratory findings.

Date	Proteins Grams.	C. H. Grams.	Total Calories	Plasma Sugar Mg. per 100 C.C.	Plasma Nacl Mg. per 100 C.C.	Blood Urea Mg. per 100 C.C.	Urine-Vol. C.C.	Urine S.G.	Urine NaCl 3m	Body Wgt. Lbs.	Remarks
May 9	Unweighed		Low	220	....	....	700	1020	515	....	Diet contained 2 gm. of salt. Thyroid 5 grains
10	Unweighed		Low	104	614	26	450	1018	412	160	Thyroid 5 grains.
11	Unweighed		Low	....	....	....	400	1016	371	....	B. P. 136/84. Thyroid 5 grains.
12	Unweighed		Low	....	....	....	650	1026	.041	159	Thyroid 5 grains.
13	Unweighed		Low	....	....	....	300	1024	049	....	Thyroid 5 grains.
14	Unweighed		Low	....	....	....	400	1026	058	156	Thyroid 5 grains.
15	Unweighed		Low	....	....	....	300	1026	062	....	Thyroid 5 grains.
16	Unweighed Discharged		Low	....	....	....	....	....	....	155	
June 3	.....	.....	.....	150	552	32	....	....	....	158	Office report.

X-ray findings. Roentgenograms were taken of the skull, pelvis, knees, elbows and hands. The skull plate shows the sella turcica to be of normal shape and size. The processus clinoideus anterior is somewhat overhanging, the posterior wall of the sella slightly indistinct. No other abnormality is observed. The pelvis is large and of typically female form. The ossa ilei are broad. The sacrum is short, broad, and triangular. The head and neck of the femur are fused, as are the greater and lesser trochanters. The lower epiphysis of the femur and the upper epiphysis of the tibia and fibula are ossified. The elbow presents the normal picture of an adult. Ossification of the lower epiphysis of the humerus and the upper epiphysis of the radius and ulna is complete. The radiogram of the hand shows closure of the lower epiphysis of the radius and ulna, and ossification of the carpal and metacarpal bones and of the phalanges. The fourth metacarpal of the right hand is shorter and broader than the third and fifth metacarpal of the same hand, and the fourth metacarpal of the left hand. This is a sign of constitutional inferiority.

According to the above history and findings, we may summarize the following symptoms pointing to a disturbance in the endocrine system: premature development of the intellect; precocious development of secondary sexual characters; onset of menstruation with obesity; hyperglycemia; lowered basal metabolism; premature closure of epiphyseal lines; infantile skeletal proportions; and a low urinary output.

DISCUSSION

Szondi has recently described an endocrine complex and certain new groups of endocrine disturbances of pluriglandular origin. He distinguishes between an endocrine asthenic and endocrine dysthenic type. The asthenic type coincides with what

is commonly known as pluriglandular insufficiency, while the latter group comprises the endocrine dysfunctions.

The first group is characterized by absence of hyperfunction of any gland, while the second group comprises glands with decreased, normal and increased functions. The subjects with undergrowth have the gland formula: depressed function of the thyroid, hypophysis and adrenals, hyperfunction of the gonads, characterized by early closure of the epiphyseal lines, normal or supernormal circumference of the skull, hypergenitalism, obesity, vagotony, schyzothymia with, in case of mental retardation, severe deficiency. Patients with overgrowth have the opposite gland formula.

This schema covers nearly entirely the clinical details of our case. However, in the analysis it is frequently difficult to decide whether a particular symptom is due to one gland or to another.

Symptoms attributable to the *thyroid* are the lowered basal metabolism, the typical coarseness and dryness of the hair and low urinary output (?). Only the two first symptoms are unquestionably of thyroid origin. Rowe emphasized particularly that in border-line values of basal metabolism the technic should be watched carefully. This was done in our case, and the three subsequent readings are a fair indication of the effect of the treatment which was followed at that time by the patient. If the lowering of the basal metabolism were not due to the thyroid it should not have responded to thyroid medication (Plaut). The hair was of the typical myxedematous type; it curiously developed coincidentally with the patient's menstruation. Puberty is the usual time of development of goiter in girls, whether as a compensatory factor of some kind is problematical. In our subject, however, puberty led to a further increase of thyroid deficiency.

The adiposity and the appearance of the skin suggest the involvement of the *hypophysis.*

Engelbach has given recently an excellent review of endocrine adiposity. We found his observations confirmed in our obesity cases due to endocrine disturbance. In this patient the fat distribution was characteristically of the girdle type. While the thorax and mammae were nearly fat free, the shoulders, arms, lower abdomen, buttocks and thighs had enormous fat

pads. The hand was slender; there was no trace of a dorsal hand pad.

The skin resembled Lisser's description of the hypopituitary skin. To quote Lisser: "The skin in hypopituitarism presents interesting changes. It is quite unlike the hypothyroid or myxedematous. It may be somewhat thick, though often it is thin, but it is not rough or scaly. It is dry and smooth as a rule, sometimes like the skin of a baby or a child."

The other symptoms which might be due to the pituitary, such as growth disturbance and retarded water metabolism, will be discussed later.

The rôle of the suprarenals is questionable. It seems fairly well established by experimental and clinical experience that the suprarenal cortex is in intimate relation with the gonads and the secondary sexual characters. Jaffe and Marine have recently shown that in rabbits destruction of the suprarenal cortex is followed by an increase of the interstitial cells of the ovary by about 70%. An analagous influence upon the testis was missing. Adler, on the contrary, found that in tadpoles only the development of the male animals was promoted. Clinical observations corroborate the promoting influence of excessive suprarenal cortex activity upon genital development.

A review of precocious puberty recently published by Reuben and Manning enumerates 21 cases with tumors of the adrenals. Other cases of precocious puberty due to the adrenals are reported by Sézary, Hamilton, Meissner and others. In all these cases a tumor was found actually at operation or necropsy. In Meissner's case the diagnosis was founded upon finding a mass in the left hypochondrium situated dorsally.

We do not find any focal symptom of a suprarenal involvement. Moreover, in nearly every case of precocious puberty due to suprarenal function the secondary sexual characteristics were of male character (hirsutism). In our patient, except for a slight mustache, which we noticed also in her mother, and which is common in Jewesses, and a few hairs between umbilicus and mons veneris, nothing of this kind was observed. It is also pointed out that in pineal as well as in suprarenal involvement the breasts are well developed but small, while in our patient the unusual enlargement of the mammae was the most disturbing symptom. The mentality, except for pineal cases, is usually

retarded or adequate to the age. In this case it was premature. A suprarenal involvement seems, therefore, improbable.

The same holds for the pineal gland. Unless there are unmistakable focal symptoms or symptoms of increased intracranial pressure or x-ray or autopsy finding, the involvement of this gland should not be considered. Misinterpretations, however, may occur, as in the case of Oesterreich and Slawyk, in which, in a cranial roentgenogram, an unequal distribution of calcaria in the parietal bones was interpreted as calcareous deposits in the pineal. The autopsy showed that though there was really calcification in the epiphysis, it was located above and behind the place where it was supposed to be.

It is doubtless true that simple atrophy may occur in any organ for unknown reasons, and hence in the two last mentioned glands. But at present the physiology and pathology of these endocrine organs is so unsatisfactorily recognized that a reference to them should be made only if the clinical symptoms are perfectly uniform and strictly point to a localized lesion.

Whether a simple primary hyperfunction of the gonads can establish itself without any further hormonal and neural stimulus is not clear from the literature. We do not include cases in which the hyperfunction is due to a malignant degeneration of the ovaries or testis (case of Sacchi and of Knopfelmacher).

An interesting contribution to the metabolic function of the ovaries was lately published by Veil and Bohn. They found that the feeding of ovarian extract affects the salt and water metabolism in normal persons, as shown chiefly in the urinary output and body weight. The effect becomes marked especially after the cessation of the administration of the extract. In this afterperiod there is a powerful hyperchloruria and polyuria, then in the following days a secondary storage of salt. It seems that the omission of the ovarian extract causes a state of dehydration, while ovarian extract causes tissue hydration. A disturbance of the salt and water metabolism is fairly plain from the patient's records. The urinary output was always low, and on salt-free diet the urinary NaCl output fell very quickly to a very low level, as if the body would retain its salt reserves with great stubbornness. This picture seems to be close to that described by Bohn and Veil.

The clinical picture suggests also hyperactivity of the ovaries. Tierney lately reveiwed this subject, citing a number of cases of precocious puberty, and inserting a differential diagnostic table of precocious puberty due to pineal, adrenal and hypergonadism. Except for the precocious mental development all the other symptoms of our subject coincided with the signs of precocious puberty following hypergonadism. Precocious mental development is a sign of pineal involvement, but since no other symptom of an epiphyseal lesion was found, all we can say is that hypergonadism can be associated with premature mental development. Cases of precocious mental development and adrenal involvement have been reported (Herzog).

The hyperglycemia seems to be of the obese type and hereditary in the family. Whether it is in any relation to the insufficiency of other glands than of the pancreas is doubtful, since Allen in particular has shown that the adrenals and the thyroid have no direct effect upon the pancreas. The hyperglycemia was easily abolished by dietary restriction.

For the complex symptoms, such as the shortness of the long bones, the premature closure of the epiphyseal lines, and the low urinary output, it is the thyroid, the hypophysis and the gonads which must be considered.

Engelbach and MacMahon have lately reviewed the osseous development in endocrine disorders. They give the age of 18 to 20 years for the union of the lower epiphysis of the ulna, lower epiphysis of femur, upper epiphysis of tibia and the upper and lower epiphysis of fibula. Except for the lower epiphysis of the fibula, for which no plate was secured, all the other above mentioned bones were found to be closed. According to the patient's history, her growth became slow at the age of 11 years and ceased entirely at 13 years. It seems, therefore, probable that the fusion of the bones occurred some time ago, possibly at her 13th year, when she stopped growing.

A juvenile hyperactivity of the anterior lobe of the pituitary gland causes gigantism, in adult age acromegaly. Shortness of the long bones is due to underfunction of the hypophysis.

While the hypophysis controls the length of the bones, the thyroid and gonads control the termination of growth. In myxedema the chondral lines remain open for an abnormally

long time. In eunuchs the growth is promoted by late fusion of the bones.

The infantile skeletal proportions which we found in our patient are rather a sign of general growth disturbance than of a particular deficiency. The undergrowth in our subject is apparently due to an anterior lobe deficiency, the early chondral fusion to the hyperactivity of the ovaries.

The water metabolism is governed hormonically by the thyroid and the gonads. Eppinger has shown in particular that the administration of thyroid extract is followed by a profuse diuresis in certain cases of edema. The myxedema is due, according to this conception, to an altered colloidal state of the tissues.

The insufficiency of the posterior lobe, or according to other views, of the infundibular region of the tuber cinereum, causes diabetes insipidus. However, it is doubtful that diabetes insipidus represents a real disturbance of the water metabolism. More and more evidence is furnished that it is due to inability of the kidney to produce a concentrated urine, which is made possible under normal conditions by an extrarenal factor so far unknown.

If we consider the work of Bohn and Veil, and on the other hand the fact that the urinary output did not increase on thyroid medication, it seems probable that the gonads are involved in this disturbance.

Therapy. The patient was treated prior to her admission to the Institute with various gland preparations for a long period of time. Thyroid had a distinct effect in that her basal metabolism became normal. The administration of pituitary and ovarian extract, even over a long period of time, had no effect.

The therapy in the Institute consisted of a low calory diet, which reduced her blood sugar to normal, and five grains of thyroid daily, which resulted in a prompt loss of weight within a week. On returning home she abandoned the diet and relapsed.

SUMMARY

1. A case of precocious puberty with hyperglycemia is described.

2. The precocious puberty is apparently due to hyperactivity of the ovaries. There are symptoms of a bilobar pituitary, thyroid and pancreatic deficiency.

3. Hypergonadism and precocious mental development can exist together.

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AN ENLARGED THYMUS IN AN INFANT; TETANY AFTER X-RAY TREATMENT

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The following case is reported because of its endocrine interest.

Baby M., male, was the fourth child born to Mrs. M., on June 26, 1922. Its weight at birth was eight pounds. There was nothing abnormal in the prenatal history of the mother, nor was the birth of the child accompanied with any difficulties. It was in all respects a normal delivery. The only abnormality about the baby was his breathing. With his first breath he developed an inspiratory crowing, which was loud enough to be heard quite a distance away. His very labored breathing was one of extreme dyspnea. At times he would even become cyanotic. The dyspnea and cyanosis would occasionally subside, or somewhat diminish, but the crowing would always persist, even during his sleep. Outside of this, no other abnormalities were found.

On July 8, 1923, Dr. S. Robins took an x-ray plate of his neck and chest and the following report was submitted to me: "There is a large, dense shadow overlapping and merging with the shadow of the base of the heart. These findings are consistent with a large thymus."

This was confirmed by another x-ray examination on July 18, 1922, at the Massachusetts General Hospital, of which I quote the following report: "Plates of the chest show markedly increased supracardiac area of dullness very suggestive of enlarged thymus."

It was clear, therefore, that the symptoms present in this baby were due to an enlarged thymus, pressing upon the trachea.

It was deemed best to treat the enlarged thymus by x-ray. Two treatments were given: one on July 17, 1922, the other about a week later. A noticeable improvement of the breathing followed these treatments. The dyspnea and cyanosis would come only when crying, while during the quiet intervals the child would breathe fairly well. This improvement continued until July 31, 1922, when the first attack of typical tetany appeared, which did not leave the patient until his death from pneumonia on March 3, 1923.

There was hardly a day when the baby would not be attacked by tetany, two or more times. The x-ray treatments were stopped for reasons to be explained later, and other therapeutic measures instituted without, however, any relief. Among drugs used were bromides, small doses of luminal, also calcium lactate in 5 gr. doses, plain, or in combination with parathyroid gland in doses of gr. 1/40 to gr. 1/20 several times a day.

In spite of being a breast baby, its gain was very slow, its weight at the time of death being about thirteen pounds, representing a net gain of about five pounds in a little over eight months.

The family history is perhaps interesting in that on the mother's side one of the parents (father) died of tuberculosis, and on the father's side a brother died of cancer. The baby's mother was an apparently healthy woman of thirty-two, with nothing abnormal in her history. Except for the first child, who had to be delivered instrumentally after three days of labor, and who died twenty-four

hours after delivery, the other two children were born normally and continued to be normal. It is perhaps of interest that on February 23, 1924, she was delivered of a baby girl with club feet, and during the latter months of this last pregnancy she developed diabetes, which promptly subsided, however, after delivery.

DISCUSSION

The important findings in this case are as follows: 1. The extreme dyspnea accompanied by crowing inspiration with the very first breath of the child; 2. An enlarged thymus, as shown by x-ray examination on two different occasions; 3. The appear-

ance of tetany in the sixth week of the baby's life, after the enlarged thymus was subjected twice to x-ray treatments; 4. The failure to relieve the tetanic attacks either by calcium lactate, or by the desiccated parathyroid substance, administered separately or combined; 5. The possible relation of thymic enlarge-

ment in this case to the malformation of the feet (club feet) in a sister born about twenty months later.

That not all enlarged thymi are apt to cause disturbance in respiration or other symptoms was shown conclusively by Liss (1), who found an enlarged thymus without any symptoms in 42 per cent of the children roentgenologically examined. Greenthal (2) also found the thymus enlarged in ninety cases, out of which eighty-seven gave no history, nor presented any symptoms of thymic involvement.

From this it would be reasonable to conclude that it is not the size of the thymus that determines the symptoms, but its relation to the trachea in the thorax, and especially in the narrow superior opening of the thorax, the so-called "critical space of Gravitz." A superficially wide thymus may give an enlarged x-ray shadow, but is not deep enough to cause pressure upon the trachea and thus produce dyspnea. On the other hand, narrow but deep thymi may show a small x-ray shadow and yet be capable of producing most severe symptoms.

Pfahler (3) arrived at a similar conclusion. After diagnosing and treating by means of x-rays a large number of enlarged thymi, he expresses himself thus: " . . . We did learn, however, that the thymus can be enlarged without producing symptoms. This is not an argument that it is a normal or harmless condition, any more than enlarged tonsils in a child are a normal or harmless condition. On the other hand, thymic symptoms may develop, we believe, even when no enlargement is shown by the x-ray. For the x-ray can only show lateral enlargement and yet it is the anterior-posterior pressure which causes the symptoms."

In this connection it is interesting to note that Smith (4) produced experimentally simulation of enlarged thymi in eight guinea pigs by injecting paraffin into the thorax in the thymic region. None of these guinea pigs suffered from any effect of the pressure by the paraffin tumor in spite of its large size, as determined by autopsy three weeks later. Of course, this experiment was no proof that a really enlarged thymus was not capable of compressing the trachea and thus producing all the dyspnea symptoms. We must not forget that the paraffin, when injected into the thorax, is in a liquid condition, and before it forms a solid mass it is therefore yielding to the normal structure of the

trachea, without compressing it. This would explain the absence of symptoms in Smith's experiments.

Now a few words as to the symptoms of tetany in our case. Was it due to the presence of an undoubtedly large thymus, or rather, as the writer thinks, to the subsequent x-ray treatments with a possible injury to the parathyroid glands? If the thymus would be responsible for tetany, why was the latter absent during the first five weeks of the infant's life, appearing only after two x-ray treatments?

I am aware of the fact that many authors consider the thymus responsible for producing tetany. Bash, as quoted by Hoskins (5), says: "Thymus plays an important rôle in the etiology of tetany." But Uhlenhuth (6) with his feeding experiments with thymus on salamander larvae (which have not parathyroids) and on the metamorphosed salamanders (which acquire parathyroids) has given, in our opinion, undeniable proof that the tetany produced in the former by thymus feeding was due to the lack of parathyroids, the internal secretion of which in some way neutralizes the toxic elements in the blood: and, vice versa, that the lack of tetany in the metamorphosed salamanders was due to the protective influences of the existing parathyroids.

It follows, therefore, that, even assuming the existence of a specific tetany toxin in the thymus, this toxin is apparently neutralized in the presence of effective parathyroids.

On the other hand, Collip and Backus (7), Grant and Goldman (8) and Barker and Sprunt (9) have shown that prolonged hyperpnea affects the carbon dioxide combining power of the plasma, thus disturbing the acid-base equilibrium of the blood, which condition, in their opinion, provokes tetany.

It would be difficult to explain the appearance of tetany in our subject as due to hyperpnea. Were it so, the tetany should have appeared much earlier in the infant's life.

It is, therefore, reasonable to assume that the x-ray treatments, while shrinking somewhat the enlarged thymus, shrunk or destroyed at the same time the sensitive apparatus of the parathyroid glands, which inevitably led to tetany. In support of this theory we will quote Grier (10), who, in discussing the preference of radium treatment in enlarged thymus, states: " . . . The difficulties in administering treatment to a small

baby are also considerable. The baby must be held by other persons who run the risk of exposure to high voltage currents and to the roentgen ray beam in their efforts to keep the patient still and in the proper position. Lead masks placed to expose the thymus area are apt to slip, and thus cause the treatment to be administered where it will do no good." If we substitute the last phrase, "do no good," by the phrase "do positive harm," it would fit our case much better.

The failure to relieve the tetanic attacks either by calcium lactate or by desiccated parathyroid gland, singly or combined, may lie in the faulty material manufactured; it may also lie in the destruction of the parathyroid hormone on its way to the blood system, via the gastro-intestinal canal, similarly to insulin, which is claimed to be ineffective when administered orally; it may finally be due to many other causes which we do not know about as yet.

The failure of calcium lactate to influence the frequency of the tetanic attacks is interesting in view of the accepted diminished calcium content of the blood in tetany patients.

As to the relation of thymic enlargements to other malformation, Greenthal (2) concludes that "patients with congenital effects and malformations are more apt to have thymic enlargement than are other patients." While in this case the baby did not have any other malformations except the enlarged thymus, it may, nevertheless, be of some significance that his youngest sister was born twenty months later with well developed club feet, an abnormal position of the feet which is ordinarily assumed by a child during a tetany attack.

To what extent this abnormality may have been a mere coincidence it is hard to say; but it may be more than coincidence that the unknown prenatal condition of the mother expressed itself in one case in an enlarged thymus, in the other, in club feet.

SUMMARY

The case is reported of an infant born with an enlarged thymus, with all the symptoms of severe dyspnea present with his first breath and with tetany following about five weeks later, after two x-ray treatments were given.

Injury to the parathyroid glands by x-ray is advanced as an etiological factor of tetany in this case.

The failure of calcium and parathyroid treatment is noted. Also the relation of enlarged thymus to other malformations in children is noted and discussed.

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Book Reviews

STUDIO DELLE SINDROMI IPERTIROIDEE NELL' ETA INFANTILE. Maria Ines Fini, Verlag L. Capelli, Bologna, 1924. Pp. 269. Reviewed in Monatschr. f. Kinderh., 1924, **29**, 191.

OUTLINE OF ENDOCRINOLOGY. W. M. Crofton. William Wood & Co., N. Y., 1924. Pp. 126.

In small compass the author of this volume has condensed much of the history, anatomy, histology, physiology, pathology and therapeutics of the glands of internal secretion. It is a book that general practitioners, or even laymen, can easily read and comprehend. Unfortunately the outline is one that should be read only by those of considerable discriminative ability, and to such readers it will have little that is new or suggestive to offer. Such statements as "in chronic infections the whole tone of the tissues can be restored by giving spleen extract" and that thymus "should always be used in rickets" are possibly true in the author's experience but have scarcely been widely demonstrated. Although thirty-one pages are devoted to the pancreas, the term "insulin" is used but once and summarily dismissed with the statement that "there are several products which have been on the market for years that will serve equally well." Likewise the author departs from orthodoxy when he states that "amylopsin, pancreatic amylase, converts cane sugar into maltose." Such excerpts suffice to show the need of reading the volume with careful discrimination.—R. J. SEYMOUR.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. Elliott P. Joslin, 1924. Lea & Febiger, Phila. & N. Y., 3 ed., Pp. 211.

Little more than an announcement of a third edition of Joslin's well-known manual is needed for readers of this Journal. The new edition continues the general plan of its predecessor but incorporates, of course, the newer work on insulin. It is written in an entertaining way, and, although it contains much technical information, is largely comprehensible to the non-technical reader. To the busy practitioner who desires as expeditiously as possible to be put in touch with the best current theory and practice in the treatment of diabetes the book should be a godsend. It should be in every health library and might well be kept on the doctor's waiting room table.—R. G. H.

AN INTRODUCTION TO THE STUDY OF SECRETION. Swale Vincent, 1924. Edward Arnold & Co., Lond. Pp. 168.

The author has brought together the chief data on a series of topics not previously all discussed in a single volume. As he states, one of the main objects was to examine the principal facts of secretion and internal secretion to see how far they may legitimately be included in a common category and thus to afford a bird's eye view of what is known of secretion as a physiological process. After a brief historical introduction, four chapters are devoted respectively to "Anatomy and histology of glands," "The physical and chemical mechanisms of secretion," certain "Special forms of secretion" and the secretions of urine, milk, skin and tears.

The last sixty-five pages of the book are devoted to the internal secretions, taking up systematically the histological and then the experimental and chemical evidences for the endocrine function of each organ. The illustrations, of which there are thirty-five, are judiciously selected and several are notably excellent. The book is written in the author's well-known lucid style and can be heartily recommended as a sound and satisfying treatise.

—R. G. H.

GOITRE: A CONTRIBUTION TO THE STUDY OF THE PATHOLOGY AND TREATMENT OF THE DISEASES OF THE THYROID GLAND. F. de Quervain; trans. by J. Snowman, 1924. William Wood & Co., N. Y. Pp. 247.

The general scope of the work can well be summarized in the author's own words. He aims "to describe those few methods which daily experience of the operation has impelled us to adopt, and to emphasize those details which are essential for a beginner to realize. We have no desire to teach surgeons who are satisfied with their own method; our remarks are only intended for those who are searching for a method, or are dissatisfied with procedures they have hitherto adopted." The book is written from Berne, Switzerland, where the author has had the advantages both of abundance of material and close touch with the methods and traditions of the well-known Swiss school.

The first seven chapters are devoted to such topics as anatomy, physiology, etiology, and so forth. The chapter on physiology is brief, and rather generalized and colorless. The author leans somewhat to the belief in a multiplicity of thyroid hormones. Two pages on the causes of goiter serve to record the author's belief that these may be numerous but that absorption of toxins from the intestines is probably the most important factor. Heredity, however, and iodin consumption are also regarded as important. An excellent objective description with

a classification of goiters is given. The attempt to correlate histological with functional deviations is specifically given up as impracticable in the present state of our knowledge of the latter. The problems involved, the author believes, are much more complicated than is assumed by the Mayo school. It is stated that the margin of safety as regards the thyroid is very wide. Much less than the traditional one-fourth of the gland substance is able to sustain normal function, and likewise the body is able to deal safely with much more than the normal amount of thyroid secretion. As a method of assaying thyroid material Stereuli's rat asphyxia test is given high rating. Its simplicity and sensitiveness would seem to commend it. The method is described on page 50. The chapter on diagnosis is detailed and well illustrated. The Goetsch test is regarded as yet uncertain and the Kottmann reaction as distinctly promising.

The latter half of the book is given over to operative treatment of goiter. Methods growing out of the author's wide experience are lucidly set forth. The book ends with a good working bibliography of nearly 30 pages.—R. G. H.

Abstract Department

The electrolyte shift in blood and tissues through adrenin action (Die durch Adrenalin bedingte Elektrolytverschiebung in Blut und Gewebe). Dresel (K.) & Wollheim (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 375-380.

Simultaneous determinations of potassium and calcium in the blood, tissues and nutrient solution containing surviving guinea-pig intestinal strips show that adrenin injections cause an electrolyte shift in the sense that calcium, and in most cases potassium also, passes into the tissues.—A. T. C.

Epinephrin in the treatment of herpes zoster. Duke (W. W.), J. Am. M. Ass. (Chicago), 1924, **83**, 1919.

Duke has had 4 years' experience with epinephrin in the treatment of herpes zoster. He has been disappointed in its effect on the vesicular lesions, but in more than half the cases it relieved the pain almost immediately, if given in adequate dosage. In using epinephrin in this condition, it is necessary to adjust the dose to suit the individual case. The dose should be pushed until the patient experiences relief or an epinephrin tremor. The amount necessary to give relief or tremor varies in different individuals from 1 minim up to several cubic centimeters—in fact, it varies in the same individual at different times almost to this extent. As a general rule, it should be given subcutaneously in doses of about 0.5 cc. at five-minute intervals, until the patient is either relieved or shows a distinct tremor. When the tremor appears, the pain in the majority of cases disappears. It usually returns in from 2 to 24 hours. The dose of epinephrin can then be repeated and continued indefinitely without injury to the patient. As a rule, it makes the use of morphin unnecessary, or at least reduces its necessity to an occasional dose.—Courtesy A. M. A.

The effect of adrenalin on the duration of the latent, the contraction and the relaxation periods of skeletal muscle at rest and undergoing fatigue. Gruber (C. M.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 335-351.

A marked decrease in the duration of the latent and contraction periods with an increased height of muscular contraction in early contraction is produced by adrenalin chloride. The relaxation period is lengthened in early contraction as well as when fatigue is coming on. The effects upon perfused, isolated non-fatigued frog's and cat's skeletal muscle are variable.—G. E. B.

Reactions of partially asphyxiated intestine to oxygen and to epinephrin. Hoskins (R. G.), & Hunter (E. S.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 143.

Intestinal segments of young adult rats suspended in Ringer's solution remained inactive until oxygen was periodically bubbled through the bath. The reactions thus initiated gradually increased and then decreased almost to zero. When adrenalin was introduced at an optimal concentration the reaction to oxygen and more especially the persisting tonus level was augmented.—G. E. B.

Experimental study of adrenal function (Experimentelle Untersuchungen über die Funktion der Nebennieren). Kisch (B.), Klin. Wchnschr. (Berl.), 1924, **3**, 1661-1663.

The adrenals were removed from rabbits by two stage operations at intervals of several weeks. The animals often survived for long periods in apparently good health. Autopsy of such animals showed neither adrenal rests nor accessory adrenals. In this connection Kisch cites Strauss' human case (1915) in which the subject enjoyed good health up to the age of 24 despite congenital total adrenal aplasia. The normality of doubly epinephrectomized rabbits is only apparent since, upon exertion, they are liable to sudden death (earlier observations confirmed by Kisch). Fettering these rabbits led to a fall in the blood sugar level rather than the characteristic rise. The weights of the adrenals of normal rabbits varied within wide limits; those of females were heavier than those of males; in more than two-thirds of the animals the left was heavier than the right (average weights, 286 and 247 mg., respectively). In most cases the gland remaining behind after unilateral adrenal extirpation was found at autopsy to be larger than probable normal. The blood sugar immediately after the operation was elevated, but after 5 hours fell below normal and after 40 hours gradually was restored. The animals gave a hyperglycemic reaction to hemorrhage, fettering or sensory stimulation, but this was less than normal in degree and was at times substituted by a hypoglycemic reaction. No significant effect of the operation on the lactacidogen or inorganic phosphorus content of the muscles could be detected, hence the weakness of adrenal deficiency is not to be explained by failure of metabolism intervening at this point. The liver was not lacking in glycogen after the bilateral operation. In two or three instances blood calcium was depressed immediately after the operation but elevated above normal later.—R. G. H.

Influence of suprarenalectomy in rabbits on antitoxin (diphtheria) formation. Marine (D.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 497-499.

With one exception the 5 animals lacking adrenals formed antitoxin as rapidly as or more rapidly than the controls, the Schick test being used as a criterion.—J. C. D.

Notes on suprarenal and pancreatic grafting. Pybus (F. C.), Lancet (Lond.), 1924, **ii,** 550-551.

Pybus reports two cases of Addison's disease, in one of which adrenal grafting was practiced with apparent success. A year after the illness began the patient had marked asthenia and bronzing and blood count of 2,200,000, but systolic blood pressure of 110. The adrenals were taken from a man who had just died of trauma. These were split and inserted subcutaneously in the patient. Ten days later the patient was able to walk 5 miles; six months later the pigmentation had disappeared. Two years later he had been for several months doing full work in a mine, after which pigmentation and weakness returned. Half of another human adrenal was then ingrafted, following which, for the past 4 years, the patient has earned his living as a hawker. At present he is slightly pigmented and has a blood pressure of 130-175 mm. In a second case nothing beyond a slight improvement in blood pressure was effected by adrenal grafting. In case of the pancreatic grafts the results were liquefaction and sloughing as would be expected, considering the rich enzyme content of the grafts.—R. G. H.

Organotherapy in Addison's disease. Rowntree (L. G.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23,** 135-136.

Nine subjects were given desiccated whole gland and epinephrin to the limit of tolerance. Each patient experienced subjective improvement. The pigmentation decreased in all. Prolonged improvement was accompanied by increase in weight, decrease in the gastrointestinal symptoms, and slight increase in blood pressure. Improvement began within one week after initiating treatment. Individual tolerance varied markedly. Intolerance was encountered in some cases.—G. E. B.

Vessel-reactions and adrenin-formation of the isolated adrenals (Gefässreaktionen und Adrenalinbildung der isolierten Nebenniere). Takenaga (K.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205,** 284-292.

The vessels of artificially perfused dog adrenals frequently do not react, but often show marked contraction with adrenin. Histamine and choline cause contraction. Perfusion of the isolated adrenals with Tyrode's solution shows in the perfused liquid an adrenin concentration up to 0.1%. The activity of the fluid does not markedly diminish with the duration of perfusion, which seems to indicate actual formation of adrenin during the perfusion.—A. T. C.

The share of adrenin secretion in the reaction to sugar puncture (Ueber den Anteil der Adrenalinsekretion an der Zuckerstichwirkung). Trendelenburg (P.), Arch. f. d. ges. Physiol. (Berl.), 1923, **201,** 39-55.

Injection into rabbits of adrenalin in amounts less than 0.05 thousandths of a milligram per kilo per minute for one hour did not affect the blood sugar height. Amounts of 0.06 to 0.1 increased the blood sugar without producing glycosuria. Amounts between 0.1 and 0.3 gave a blood sugar value at the end of the first hour averaging 0.2%, with in many cases, glycosuria. Amounts above 0.3 almost always gave glycosuria. The adrenin content of the adrenals after puncture makes it probable that the adrenin output is responsible for the increase in blood sugar after puncture. In two experiments after puncture the adrenin output from the glands was above 0.5 thousandths milligram per kilo per minute, which is high enough to produce glycosuria within a short interval.—A. T. C.

Fundamentals of organotherapy. Asher (L.), Klin. Wchnschr. (Berl.), 1924, **3**, 1705-1708.

Asher discusses the difficulties of a scientific foundation for organotherapy. The conceptions of hypofunction and hyperfunction are—even in the best studied instances **(thyroid)**—to a large degree artificial constructions. In other cases—excessive production of **epinephrin** or of **pancreatic** secretion—such assumptions are so far merely speculations. It is different, whether the action of a hormone increases in a simple proportion to the amount injected or in a curve which reduces the interval between the threshold and the maximum of action. The matter is further complicated by the possibility of a change into the opposite action after this maximum is reached—for instance, the stimulating effect of small doses of thyroid preparations or of epinephrin on the automatic movements of the intestine and bladder, and the inhibiting action of large amounts. The point of this reversal depends on the condition of the tissue—not merely on the dosage. Asher produced with Mauerhofer experimentally in rats the extreme muscular weakness which is characteristic of **Addison's disease.** Yet organotherapy fails completely in this disease. He believes that the mechanism may be analogous to that demonstrated by Carlson and Luckhardt in **parathyroidectomized** animals. The endocrine function of the **pituitary** gland is doubtful, except perhaps in phenomena connected with **acromegaly** and **gigantism.** This does not, however, detract from the therapeutic value of its preparations in obstetrical cases and in **diabetes insipidus.**—J. Am. M. Ass., **83**, 1380.

Glandular therapy. Billings (F.), J. Am. M. Ass. (Chicago), 1924, **83**, 1000-1001.

Billings states that at the present time substitutional organotherapy alone seems to be based on substantial grounds, and this principle is of practical value only to a limited degree. The use of **thyroid** gland or of thyroxin in proper doses will overcome the results, partially or wholly, of deficiencies of the thyroid gland secre-

tion. **Insulin** used daily and properly will restore and maintain carbohydrate metabolism in conditions due to deficiency of the internal secretion of the **pancreas.** But substitutional organotherapy in morbid conditions of man or animals due to deficient secretion of the glands of internal secretion, by the oral administration of the fresh gland tissues or of dried or otherwise prepared glands, is in an unsatisfactory status. This is due in part to the fact that the active principles of the secretions of all the glands of internal secretion, with the exception of the thyroid, are apparently destroyed by the digestive juices of the stomach and bowel. **Pituitary** extract and **epinephrin** must be considered as pharmacodynamic preparations, because, up to the present time, the various preparations of pituitary and epinephrin do not appear fully to take the place of the glands themselves. It must be said, however, that pituitary extract appears to substitute for the gland for temporary periods. With the exception of thyroxin and insulin, the use of preparations of other glands of internal secretion, hypodermically or intravenously, has not afforded uniform and consistent results that can be definitely ascribed to the specific efforts of the internal secretions of the glands. However, it must be stated that the possible good effects of the administration of preparations of the glands of internal secretion subcutaneously or intravenously may be masked by the reactions of the body to a foreign protein administered in the same manner. Substitutional organotherapy by the transplantation of fresh gland substance has been successfully accomplished, but the length of time during which engrafted tissue retains its specific character and function is variable and uncertain, and the results have been of short duration and of limited value. The present furore of transplantation of the **gonads** for rejuvenation, and especially for the restoration of sexual potency in senile individuals, Billings says is attended with such manifest lack of scientific experimental spirit and methods and is so tinctured with commercialism as to make this practice under present knowledge a professional disgrace. Substitutional organotherapy is embarrassed, too, by the difficulties attending the recognition and interpretation of the symptoms and signs due to the deficiency of the secretion of a single gland. These difficulties are intensified in the case of syndromes due to multiglandular deficiencies and in the necessary differentiation between the morbid conditions due to deficiencies of secretions of the internal glands and deficiencies in growth, development and other morbid condition due to want of sunlight and a properly balanced diet. At present, substitutional organotherapy in the treatment of conditions alleged to be due to deficiencies of the glands of internal secretion, with the exception of the thyroid and pancreas, cannot be utilized in general practice with the hope that definite results will be obtained. The brilliant results attending the use of preparations of the thyroid, including thyroxin, and of insulin afford reasonable belief that other

important glands of internal secretion will be found to yield active principles that will arm us with specific agents for the correction of morbid conditions due to deficiencies of secretion of the respective glands. In the meantime, recognizing our responsibility to the public in this as in other matters that affect the welfare of the people, we should not continue to patronize and support those manufacturers of glandular remedies who make statements of specific virtues possessed by pluriglandular preparations that are without foundation of fact. The existence and continued pernicious influence of the manufacturers of glandular products who publish statements of their therapeutic value without the support of established physiological and clinical facts will depend on whether the medical profession will patronize them. A decided forward step would be taken if physicians were to limit their use of animal organ preparations to those admitted to the United States Pharmacopeia and the current edition of New and Nonofficial Remedies.—Courtesy A. M. A.

The effect of endocrine feeding upon the learning performance of white rats. Blatz (W. E.) & Heron (W. T.), J. Exper, Psychol. (Lancaster), 1924, **7**, 291-311.

Blatz and Heron investigated the effects of feeding desiccated **adrenal** and **pituitary** substance (anterior lobe) to rats. The criteria of effects were solution of mazes and performance in problem boxes. The pituitary-fed rats were rather more, and the adrenal-fed rather less, efficient than the controls. The pituitary-fed showed slightly better growth. Reproduction was suppressed during the pituitary feeding.—R. G. H.

Endocrine therapy in infancy and childhood. Howland (J.), South. M. J. (Birmingham), 1924, **17**, 743-749.

Howland says: The conclusion is forced on us, and it is a conclusion to which physiologists and pharmacologists will subscribe, namely that if we use single extracts in pediatrics we are confined to the treatment of two conditions, **thyroid** deficiency and **diabetes.** Uniglandular therapy then is, in generel, unsatisfactory. Pluriglandular therapy has come into being on the supposition that not infrenquently there is a disordered activity of several glands, a failure of coordination among them. For the belief that numerous glands may be affected in such ways as to produce various clinical syndromes there is no pathologic proof available. Similarly, there is no chemical or physiologic proof of the existence of such conditions. The fact that gradual improvement follows the administration of a heterogeneous mixture of gland extracts is not sufficient evidence to prove that a gland or group of glands is the cause of a clinical picture. One must demand a striking and almost immediate change. One must also demand pathologic or physiologic or chemical evidence. The clinician of the present day is in danger of

losing his clinical sense and his critical judgment. He leans too much on laboratory methods for his diagnosis.

—J. Am. M. Ass., **83**, 1797.

Relation between the spleen and liver (Die Wechselwirkung zwischen Milz und Leber). Kobayashi (M.), Biochem. Ztschr. (Berl.), 1924, **151**, 491-497.

Aceton is formed when sodium butyrate is perfused through the liver of guinea pigs. This is increased from two- to three-fold when extract of spleen is added. It is not affected by extract of the intestinal wall which contains cholin as does splenic extract.—F. S. H.

Blood calcium and the endocrine glands (Die endokrinen Drüsen und der Blutkalk). Leites (S.), Biochem. Ztschr. (Berl.), 1924, **150**, 183-193.

In dogs and rabbits it was found that the normal blood calcium ranges within narrow limits and that the glands of internal secretion play an important rôle in its maintenance. The removal of the **thymic** and **parathyroid** function causes the blood calcium to decrease. The effect of thymectomy is slow in appearing; that of parathyroidectomy more rapid. When the **thyroid** and **gonads** are removed there is a tendency for the blood calcium to increase in amount. Opotherapy with thymus, thyroid and **testicular** preparations, which in the normal animal brings about no response, causes in the defective animal the return of the blood calcium to the normal level. Thymectomy in young dogs retards growth.—F. S. H.

The frequency of endogenous endocrine obesity and its treatment by glandular therapy. Lisser (H.), Calif. & Western Med. (San Fran.), 1924, **22**, 509-513.

Overeating and insufficient exercise often cause exogenous obesity. The great majority of obese individuals are not fat for these reasons only. **Hypothyroidism, hypopituitarism** and **hypogonadism** are not uncommon, especially in mild degree, and are almost invariably characterized by adiposity. The importance of endocrine dysfunction in producing obesity directly, and in indirectly causing the symptoms that lead to obesity (abnormal appetite and physical inertia) should be recognized in diagnosis and in planning treatment. Basal metabolic rates are valuable, but not the sole index for institution of glandular therapy. A normal rate is not necessarily a contra-indication to the administration of thyroid extract, but its use should be checked by frequent rate determinations. Pituitary extract alone will sometimes reduce weight. Weighed diets are rarely necessary. Reasonable restriction of fats and carbohydrates is more practicable, less irksome, and usually suffices in conjunction with the proper endocrine therapy. The obesity of childhood and adolescence is usually of endocrine origin.

One should be cautious in any and all methods of reduction in patients over 50. There is no royal road to reduction, whether it be by diet cure, victrola cure, roller cure, or gland cure. Each case requires individual study.—Author's Summary.

The clinical value of basal metabolism determinations (Sobre el valor clinico de la determinacion del metabolismo basal). Marañon & Carrasco, Arch. de med., cirug. y espec. (Madrid), 1923, **9**, 385-410.

The authors have observed the basal metabolism in 177 cases. In 44 cases of **hyperthyroidism** more than 20% showed augmentation. In case of 19 neurotic subjects with disorders principally in the vegetative functions, together with some loss of weight and even a slight increase in the size of the thyroids, contrary to certain American authors, Marañon found the basal metabolism of little value in differential diagnosis. In 4 cases of paroxysmal tachycardia the metabolic findings excluded the involvement of hyperthyroid factors. In 11 cases of hypothyroidism in all its forms, and in 4 cases of **myxedematous infantilism** the metabolism was always below normal; in 3 cases of simple goiter, normal; in 15 cases of obesity, always low; in a case of juvenile arthritis deformans without endocrine symptoms, normal; in 21 cases of menopause, very variable, depending on the functional state of the thyroids; in 2 cases of surgical menopause low figures were observed. The authors noted 24 cases of juvenile **ovarian** insufficiency with metabolism of a low type, and 5 cases in which it oscillated between plus 10% and plus 50%. The figures obtained in 4 cases of **acromegaly** are very interesting. In two the metabolism was from plus 20 to plus 50. In the third—an old acromegalic—there was an enormous **pituitary** tumor with beginning obesity. The metabolic figure was normal, plus 2%. In the last case—acromegaly with myxedema—the result was minus 27%; this case demonstrates how two distinct endocrine influences are able to work inversely, the thyroid always seeming to be the more dominant factor. In 2 cases of hypophyseal obesity (Fröhlich's syndrome) the metabolism was normal, although of a low type. In 3 cases of puerperal **pseudo-hermaphroditism** and in 2 cases of adiposity and **dwarfism** the figures were low. In a case of **diabetes insipidus** the metabolism was plus 12%, and in 1 case of lipodystrophia progressiva it was normal. The authors observed a case of precocious senility with a metabolism of minus 4%, and another of cachexia of unknown cause, perhaps hypophyseal, of minus 12%. In 3 cases of **Addison's disease** which came under their observation the hypometabolism generally referred to was not confirmed. In 2 cases of pseudo-Addison's disease and in a case of Recklinghausen's disease the figures were normal. Also in 3 cases of **diabetes** and in one of essential hypertension the metabolism was normal.—E. B.

A case of Barraquer's disease (Un caso de enfermedad de Barraquer). Pardo, Endocrinol. & Nutrition (Madrid), 1924, **2**, 103-107.

The author describes a typical case of lipodystrophia progressiva in a girl of 14 years. Several endocrine symptoms were observed: hypogenital hands, asthenia, melanoderma in nose and cheeks, and amenorrhea. The basal metabolism was plus 10%. Pardo thinks that this syndrome ought to be called "Barraquer's disease," since Barraquer first described it.—E. B.

Metabolism observations in a case of urticaria scripta. Rowe (A. W.) & McCrudden (F. H.), Boston M. & S. J., 1924, **191**, 60-61.

A married woman of 36 presented the following abnormalities: marked anidrosis; lymphatic hyperplasia; itching skin; skin dryness; urticaria scripta; subnormal temperature; low pulse rate; low blood pressure; subnormal basal metabolism; albuminuria with rare casts but without impairment of renal function, and without increased non-protein nitrogen in the blood; slight secondary anemia; urine low in quantity, solids, and nitrogen; subnormal vital capacity, carbon dioxide in alveolar air, blood urea, and blood uric acid. With all the signs and symptoms pointing to disturbance in the sympathetic nervous system, and all of them such as have been described in cases of hypothyroidism, it seems probable that this case is one of endocrine imbalance with the **thyroid** chiefly involved. It is suggested that all such cases should be studied with this possibility in mind.—R. G. H.

Hormones and the pH. Zondek (H.) & Ucko (H.), Klin. Wchnschr. (Berl.), 1924, **3**, 1752-1753.

Zondek and Ucko tested the influence of **thyroid** extracts on the metamorphosis of tadpoles in various concentrations of hydrogen ions. They found a minimum between 7 and 7.7 pH (about the pH of the blood) and a marked action between 6.4 and 7. They believe that the hormones are inactive in blood because of its reaction, and are "tuned in" at the periphery by changes of the concentration of various ions, including hydrogen and hydroxyl. This may account for the difficulty in demonstrating biologically the presence of hormones in the blood.—J. Am. M. Ass., **83**, 1465.

The follicular hormone of the hen ovary. Allen (E.), Whitsett (J. W.), Hardy (J. W.) & Kneibert (F. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 500-503.

The ovarian follicular hormone can be extracted from ovaries of laying hens. Injected into spayed rats it causes estrous growth in the genital tract. Extracts of full sized follicles, eggs from the oviduct, fresh eggs (also whites and yolks separately), and 5-, 10- and 14-day embryos with their membranes have given negative

results. These experiments establish the expected non-specificity of the follicular hormone as concerns birds and mammals.—J. C. D.

The physio-pathological significance of interstitial cells (De la signification physiopathologique des éléments interstitiels). Brugnatelli (E.), Arch. ital. di biol. (Pisa), 1922, **71**, 120-132; see also, Folia gynaec. (Pavia), 1922, **15**, 105-116.

Various observations on the so-called mast-lipoid cells, the interstitial tissue of the **mammary** gland, and the culture in vitro of the **ovary** indicate that the interstitial cells form part of a system of elements practically present in the whole organism, and capable of further development and multiplication under certain physiological and pathological conditions; in the author's opinion, however, their precise function is not known.—Physiol. Abst., **9**, 362.

Glandular therapy: Physiology of the mammalian ovaries. Carlson (A. J.), J. Am. M. Ass. (Chicago), 1924, **83**, 1920-1923.

Carlson asserts that at present there is no reliable evidence that ovarian extract effects are specific for the ovary. Until it has been conclusively shown in spayed females that these extracts prevent the atrophy of the uterus and initiate and maintain estrual periods typical for the species, it seems clear that experimental ovarian organotherapy has not been placed on a scientific basis. The reasons for the past failures may be inherent in the complexity of the ovarian hormones and their practical failure to be active when given by mouth; but the ovarian field can point to no such persistent and systematic work of hormone isolation as we have in the case of the **thyroid** and the **pancreas**. The sex life of the mammalian female is developed and maintained by the ovaries through continuous and temporary hormone mechanisms. Hormones acting more or less continuously develop and maintain the secondary sex organs and act to increase basal metabolism; temporary hormones from ripe follicles and corpus luteum initiate the estrual cycle, the early interaction between the fertilized ovum and the uterine mucosa, mammary gland hyperplasia and suppression of follicular growth. Menstruation appears to be only indirectly dependent on the follicular and luteal hormones, in that it follows failure of fertilization and atrophy of corpus luteum spurium. But the hormones initiating estrus are necessary precursors to menstruation. The initial cause in all menstrual disorders may be outside the ovaries and hence not to be affected by ovarian therapy. None of the ovarian hormones has so far been isolated, as determined by reliable biologic or chemical tests. And it is still an open question whether in the experimental animals any of the ovarian functions can be maintained by substitution therapy; that is, by feeding or injection of ovarian extracts.—Courtesy A. M. A.

New studies on folliculin. Passage of the hormones through the placenta (Nouvelles recherches sur la folliculine. Contribution à l' étude du pasage des hormones au travers du placenta). Courrier (R.), Compt. rend. Acad. d. sc. (Par.), 1924, **178**, 2192-2193.

Follicular liquid from the ovaries of the cow or sow, injected into guinea pigs, castrated (spayed) 8 months before and therefore in complete genital repose, caused within 48 hours the modifications of the vagina characteristic of heat, as shown by an active proliferation of the epithelial cells. One cc. of follicular liquid was injected into a pregnant guinea pig on each of the last 4 days of the term. A few hours after delivery one of the young was killed and examined histologically, when a rapid proliferation of the epithelial cells of the vagina was evident. Control animals showed no such vaginal activity. It is therefore concluded that the follicular hormone passes through the placenta.—Chem. Abst., **18**, 3067.

Sex reversal following ovariotomy in the fowl. Domm (L. V.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 28-35.

Both ovaries were removed from Brown Leghorn hens before egg laying began. The birds then came to resemble males in action and appearance. Autopsy showed masses at the ovarian site which on section proved to be immature testicular tissue.—J. C. D.

The extraction and some properties of an ovarian hormone. Doisy (E.), Ralls (J. O.), Allen (E.) & Johnston (C. G.), J. Biol. Chem. (Balt.), 1924, **61**, 711-727.

A method of extracting a hormone from the liquor folliculi which induces full estrous growth in the tissues of the genital tract is described. The yield in rat units from liquor folliculi is compared with the yield from other tissues. These results emphasize the physiological importance of the graafian follicle in the second cycle. A few properties of the hormone are given and data are cited to show that the activity of the follicular hormone is not associated with cholesterol color reactions.—F. S. H.

Influence of qualitative underfeeding on the function of the genital glands (Einfluss qualitativer Unternährung auf die Funktion der Keimdrüsen). Eckstein (A.), Arch. f. d. ges. Physiol. (Berl.), 1923, **201**, 16-24.

A diet deficient in fat, vitamin A, and phosphorus led to atrophy of testes and failure of spermatogenesis in male rats. The testes showed marked degeneration, which extended to the interstitial cells. The ovaries of female rats did not appear to be affected, though conception did not occur.—A. T. C.

A case of precocious puberty. Hutchinson (R.) & Wauhope (G. M.), Brit. J. Child. Dis. (Lond.), 1924, **21**, 57-62.

A girl of 3½ years of age began menstruating at 17 months and has been having irregular periods since then of the 28 day type, and lasting 2-3 days. She has pubic hair, which first appeared with the onset of menstruation, enlarged breasts, no axillary hair, a harsh voice, and is mentally bright and overgrown. She has no control over her bladder. No tumors were felt either on abdominal examination or by vaginal palpation of the **ovaries.** X-ray examination showed premature ossification of the skeleton and closure of the epiphyses; there was no indication of any tumor formation in the skull. The authors think the condition is due to ovarian hypersecretion, although they had no chance to prove their belief because of the refusal of the parents to permit operation.—M. B. G.

The relation of the female gonads to renal diabetes (Die Beziehung der weiblichen Keimdrusen zum renalen Diabetes). Küstner (H.), Arch. f. Gynäk. (Berl.), 1924, **122,** 282-309.

Clinical and experimental studies showed that renal diabetes occurs during pregnancy in both man and animals. This sensitivity of the kidneys disappears towards the end of pregnancy in human beings. Glycosuria occurs in non-pregnant women a few days before menstruation and in animals at estrus. Removal of the **ovaries** is followed by disappearance of renal diabetes. This does not occur when the uterus is removed. When ovaries from pregnant are implanted into non-pregnant animals there occurs a diabetes of one day. All these phenomena are interpreted as showing that renal diabetes is associated with a functioning **corpus luteum.**—F. S. H.

The effect of light doses of alcohol upon the estrus cycle and on number of corpora lutea and prenatal mortality in the mouse. MacDowell (E. C.), Proc. Soc. Exper. Biol & Med. (N. Y.), 1924, **21,** 480-485.

Mice were exposed to the fumes for 45 minutes each day, by enclosure in a pint milk bottle with a piece of filter paper soaked in 95% alcohol. It was concluded that the alcohol treatment had no effect upon the reproduction of the mice studied when judged by the following criteria: (1) age of opening of the vaginal orifice; (2) age at first estrus; (3) length of estrus cycle; (4) number of corpora lutea per ovulation; (5) prenatal and natal mortality; (6) number of living young per litter.—J. C. D.

Transplantation of the ovary in old animals (Innesti di ovaia in animali vecchi). Pettinari (V.), Boll. d. Soc. med.-chir. di Pavia (Milano), 1924, **36,** 163-169.

Preliminary note regarding two experiments. The first was carried out on a bitch about 17 years old, which showed all signs of senility, and in which the ovary of a young dog was transplanted endoperitoneally. A few months afterwards the bitch exhibited

remarkable phenomena of rejuvenation, including the reappearance of sexual activity. About 13 months after the operation she gave birth to 5 normal puppies, 4 of which she was able to suckle. The second experiment was carried out on a dog 12 to 13 years old, which also showed signs of advanced senility, and could hardly be made to move from its kennel. The ovary of a young bitch was grafted between the two layers of the tunica vaginalis, as suggested by Voronoff for the transplantation of the **testis.** A few months afterwards this animal likewise exhibited phenomena of rejuvenation, including the return of sexual activity.—Physiol. Abst., **9,** 410.

Influence of ovaries on metabolism (Uber den Einfluss der Keimdrüsen auf den Stoffwechsel). Plaut (R.) & Timm (H. A.), Klin. Wchnschr. (Berl.), 1924, **3,** 1664-1666.

In 5 cases women were sterilized by radiation. At the onset of amenorrhea the basal metabolism was depressed 100-300 calories but later returned to normal. The authors theorize to the effect that compensatory **thyroid** activity is ultimately set up.—R. G. H.

Osteomalacia in China. Wampler (F. J.), China M. J. (Shanghai), 1924, **38,** 349-357.

This disease, which is common in North China, is attributed to dietary deficiency. Cures or great improvement in all cases were obtained by the use of cod-liver oil and calcium. The theory that osteomalacia is due to "a tropho-neurosis of **ovarian** origin" is considered to be untenable.—L. G. K.

Macrogenitosomia precox in a girl 9 years of age (Sindrome de macrogenitosomia precoz en una niña de nueve años). Burghi, Arch. espan. de pediat. (Madrid), 1923, **5,** 257-271.

The patient, the daughter of an alcoholic father, after an attack of measles showed clearly defined hydrocephalus. She presented rachitic deformities in the thorax and lower extremities, cyanosis in the hands and feet and, ultimately, macrogenitosomia precox. Her height was 1.34 meters. The axillary hair and the **mammary** glands were completely developed. The author suggests that the macrogenitosomia is of epiphysial origin, but the deformity of the sella turcica, the symptoms of adolescent dystrophy and the adiposity seem to indicate that the normal function of the hypophysis is altered. The author is unable to explain the mechanism of the dystrophic phenomena provoked by the epiphysial tumors without the intervention of the incretory glands. This case in which there was no symptom of tumor suggests that the hypophysis had undergone precocious changes in consequence of the hydrocephalus and the accompanying intracranial hypertension upholds this interpretation.—E. B.

Contribution to the pharmacology of extracts of the posterior lobe of the pituitary gland. Kolls (A. C.) & Geiling (E. M. K.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 67-81.

The effects of intravenous doses of pituitary extract were studied in anesthetized and unanesthetized animals. In the unanesthetized dog the circulatory changes were: rise of mean blood pressure, decrease in pulse pressure, marked slowing of the cardiac rate even after vaginal influence has been removed by atropine, decrease in minute volume output of the heart, cardiac dilatation, paling of the skin and visible mucous membranes. The unanesthetized animals showed periods of apnea and marked reduction in consumption of oxygen. These changes were all less marked in the etherized animals. Immediately following the pituitary injection for a brief period the Hb. of the blood was increased.—G. E. B.

The diuretic and antidiuretic effect of pituitary extract and suggestions for a subsidiary test. Mackensie (W. G.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 83-99.

The inhibition of the flow of urine when collected from the bladder or lower ureter following pituitary injection is due to contraction of the smooth muscle of bladder or ureter or, with large doses, to a vascular effect on the kidney. The diuretic response is accompanied by a change in the distribution of water in the body but the hydremia outlasts the diuresis. The antidiuretic effect requires larger doses than that sufficient to produce diuresis but repeated small doses may have the effect of summation. It is not proved that the antidiuretic effect is produced elsewhere than in the kidney. A method of procedure for testing the diuretic properties of pituitary extract is given.—G. E. B.

Papilloneuritis in children with hypophyseal syndromes and their treatment by hypophysis and thyroid extracts (Algunas observaciones de papiloneuritis en niños con sindromes hipofisarios y su tratamiento por la hipofisis-tiroidina). Muñoz (U.), Union med. (Zaragoza), 1923, **250**, 97-99.

Two children with typical Frölich's syndrome and papilloneuritis were cured of the general syndrome and of the ocular lesions by administration of whole hypophysis extract alternated with injections of thyroid extract.—E. B.

Some factors concerned in the deterioration of pituitary extracts. Smith (M. I.) & McClosky (W. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 138.

Fresh infundibular lobes carefully dissected from pituitary glands removed soon after the animal is killed may be kept for at least 2 months at a temperature of -10 to -17 degrees C. without

loss of oxytocic activity; at about 0 degrees C. their activity deteriorates rapidly after 2 weeks. Extracts carefully prepared from fresh infundibular material or from standard powder and sterilized at 100 degrees C. were found to retain their oxytocic activity for one year when kept in a cold room; kept in the laboratory they showed no loss up to 8 months in either oxytocic or pressor activity. Temperatures of 45 to 60 degrees C. cause deterioration. The deterioration of pressor and oxytocic activities runs parallel. This is regarded as contributory evidence of the chemical identity of the two principles.—G. E. B.

Insulin and diabetes insipidus (Insulina e diabete insipido). Villa (L.), Boll. d. Soc. med.-chir. di Pavia (Milano), 1924, **36**, 281-288.

The experiment was carried out on a patient who had been affected for years by diabetes insipidus due to a lesion of the pituitary body, and who had been repeatedly treated with pituitary extracts. After the administration of insulin the polydipsia disappeared, and the quantity of urine eliminated in 24 hours fell from 12 to 2 litres. The total blood volume grew during the first day of treatment, but diminished during the following ones. In spite of the simultaneous large administration of glucose the subject had two very severe hypoglycemic crises which lasted for many hours in spite of repeated injections of adrenalin. The polyuria did not reappear when the insulin treatment was stopped, but it is not stated for how long.—Physiol. Abst., **9**, 393.

Chemical regulation of the heart by the liver (Die chemische Regulation des Herzschlages durch die Leber). Asher (L.) & Takahashi (K.), Biochem. Ztschr. (Berl.), 1924, **149**, 468-490.

Apparently there is produced by the liver a hormone which acts upon the heart in the nature of a sympathetic stimulant.—F. S. H.

Diabetes accompanied by infantilism treated with insulin for a year (Diabète avec infantilisme traité de suis un an par l'insuline). Apert (E.), Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 894-895.

The patient was a young man. The glucosuria was reduced from 200 grams to from 0 to 20-30 grams. Growth was resumed in stature and weight, as was development of the sex organs.—F. S. H.

Observations on the use of insulin in nondiabetic children. Barbour (O.), Illinois M. J. (Oak Park), 1924, **46**, 131-133.

The author has had apparently good results from the use of insulin in 12 nondiabetic children suffering with the following conditions: malnutrition, 2; malnutrition with tuberculosis, 2; malnutrition with chronic bronchitis, 3; marasmus, 1; acute inanition, 1; acute nephritis, 2; normal infant, 1.—I. B.

A practical danger in the use of insulin by the patient at home. Berghoff (R. S.), J. Am. M. Ass. (Chicago), 1924, **83**, 1308-1309.

When insulin was first introduced, Berghoff recalls, it was deemed advisable that its administration be begun with the patient under hospital supervision. When insulin therapy is prolonged indefinitely, its administration by the patient himself becomes necessary. We have felt safe in assuring our patients who possess urine sugar in appreciable amount that its entire absence on a given diet and set insulin dosage bespeaks a corresponding satisfactory blood sugar level, and calls for at least a temporary cessation of insulin therapy. In fact, we had almost accredited insulin with a gradual resumption of carbohydrate tolerance. However, at first sporadically, and of late regularly, we have been impressed with the undeniable fact that after a more or less continued course of insulin the blood sugar threshold rises appreciably. This rise of the blood sugar threshold is of significant importance to the patient, robbing him of his only check, and lulling him into a sense of false security. If, for example, before the initial use of insulin, a patient's blood sugar threshold is determined at from 0.120 to 0.150, at which point sugar appears in the urine, it has been our common observation that the use of insulin soon raises those figures materially, in some instances more than 0.50 point. The practical significance is obvious. If patients are to be entrusted with the home use of insulin, a rough check on their status is essential. A daily blood sugar test is not practical. In the past we relied on a daily urine sugar estimation to afford that information. In view of the recent gross discrepancies, however, between blood and urine sugar levels, that would seem unsatisfactory.—Courtesy A. M. A.

Some effects of insulin on the carbohydrate and phosphorus metabolism of normal individuals. Blatherwick (N. R.), Bell (M.) & Hill (E.), J. Biol. Chem. (Balt.), 1924, **51**, 241-259.

Insulin administered to normal subjects before glucose ingestion causes a marked decrease in the inorganic phosphorus of blood plasma. The rate of excretion of phosphorus in the urine is greatly lessened at the same time. These changes occur during the period of hypoglycemia. When insulin is superimposed upon a standard diet the rate of excretion of phosphorus is altered to a large extent. The relation of these findings to carbohydrate metabolism is discussed. They bring additional support to the hypothesis that a combination of hexose with phosphoric acid is an intermediate product in the metabolism of carbohydrate. The excretion of normal urine sugar is not appreciably affected by the injection of insulin.—F. S. H.

Studies of intermediary carbohydrate metabolism in the liver by determination of the gas exchange (normal, hunger, insulin action

and pancreas deficiency) [Studien über intermediären Kohlenhydratunsatz an der Leber bei gleichzeitiger Verfolgung des Gaswechsels (Norm, Hunger, Insulinwirkung, pankreoprive Leber). VII.]. Brugsch (T.), Horsters (H.) & Shinoda (G.), Biochem. Ztschr. (Berl.), 1924, **151**, 318-334.

The respiratory quotient of the dog liver lies between 0.51 and 0.68. In conditions of pancreatic diabetes the value ranges from 0.73 to 0.79. The oxygen need or consumption of the liver in the latter case is extraordinarily low, being but 1.0 per gram of protein, while that of the normal organ is around 2.2. Insulin in vitro increases the oxygen consumption of the liver but not up to the normal value.—F. S. H.

Intermediary carbohydrate metabolism in phloridzin diabetes during hunger and under insulin treatment (Studien über intermediären Kohlenhydratumsatz beim Phlorrhizindiabetes, im Hunger und unter Insulin. V.). Brugsch (T.), v. Exten (S.) & Horsters (H.), Biochem. Ztschr. (Berl.), 1924, **150**, 49-59.

Sugar formation in starved, phloridzinized animals is exhibited by the kidneys, liver and heart musculature; body musculature falls behind in this respect. The sugar is apparently derived from fat. Insulin does not seem to interfere in this process. Phloridzin diabetes differs from pancreatic diabetes in that in the former sugar is primarily formed in the kidneys, while in the latter the liver plays the major role. In the latter condition the ability to form sugar is not lost, but that of oxidation is. In the former condition (phloridzin diabetes) oxidative capacity is not necessarily lost, but the sugar-forming ability of the kidneys is heightened.—F. S. H.

A comparison of the rate of glycolysis in different bloods with special reference to diabetic blood. Cajori (F. A.) & Crouter (C. Y.), J. Biol. Chem. (Balt.), 1924, **60**, 765-775.

The rate of glycolysis in bloods of widely different sugar content incubated at 38° C. under sterile conditions was determined. It was found that the rate varies directly with the amount of sugar present, but that there is a marked deviation from the rate predicted by the monomolecular reaction velocity equation. No evidence was obtained which indicated a diminution of glycolytic power in diabetic blood. The effect of potassium oxalate in decreasing the rate of glycolysis has been found to be especially pronounced in diabetic blood.—F. S. H.

Atrophic sclero-gummous pancreatitis and syphilitic retro-peritoneal callosity (Pancréatite atrophique scléro-gommeuse et retro-péritonite calleuse syphilitiques). Carnot (P.) & Peron (N.), Bull. et mém. Soc. méd. d. hôp. d. Par., 1924, **48**, 1315-1318.

The patient showed almost complete destruction of pancreas but no diabetes.—F. S. H.

Insulin and phlorhizin glycosuria. Colwell (A. R.), J. Biol. Chem. (Balt.), 1924, **51**, 289-301.

Two experiments are described in which phlorhizinized dogs were kept running steady glucose excretions for 6 days each, finally completing the experiment in good physical condition. These dogs were given injections of iletin, three in all, with resultant depressions in the output of sugar.—F. S. H.

The influence of insulin on phlorhizin poisoning. Cori (C. F.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 99-106.

Insulin causes a fall in blood sugar in completely phlorhizinized rabbits, but the power of blood sugar regulation is not lost. A marked diminution in the sugar excretion is brought about. Sugar formation from proteins is not affected and the nitrogen excretion is not diminished.—G. E. B.

Comparative study of the sugar concentration in arterial and venous blood during insulin action. Cori (C. F.) & Cori (Gerty T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 72-73.

Glucose was injected into rabbits and simultaneous samples of blood from the femoral artery and vein were analyzed to find how much glucose had been absorbed by the muscles. Then insulin was added to the glucose solution injected. The 8 observations reported show an average increase of nearly 60% in the amount of glucose absorbed.—J. C. D.

Insulin from the codfish. The direct application of picric acid to the islet tissue. Dudley (H. W.), Biochem. J. (Liverp.), 1924, **18**, 665-668.

A convenient method of extracting insulin from the islet tissue of the codfish is described. It consists of applying picric acid directly to the tissue, extracting the insulin-containing picrate fraction with watery acetone, and converting the picrate into a soluble hydrochloride as described in a previous paper. From the islet tissue of the cod, although collected from fish which had been caught at varying intervals up to 24 hours previously, a yield of about 12 rabbit units per gram of tissue was obtained. The islet tissue of the cod contains, weight for weight, apparently ten times as much insulin as does mammalian pancreas.—F. S. H.

The action of insulin on different carbohydrates (Recherche au sujet de l'action exercée par l'insuline sur les différents hydrates de carbone). Enselme (J.), Thèse de Lyon, 1924; abst., Presse méd. (Par.), 1924, **32**, 752.

In this research, carried out under the direction of Hugounenq, the author studied the chemical composition of insulin and its effect on various carbohydrates. Using insulin prepared according to the method of Chabanier (the activity of which was verified on rabbit), a crystallized body was obtained which had no effect on glycemia. The investigations of Hugounenq and Enselme show that the direct action of insulin in vitro on carbohydrates is negative. Negative results were likewise obtained when the reaction was made in the presence of blood serum or organ extracts, such as liver or lung. On the contrary, insulin modifies the action of certain blood ferments. For instance, it clearly increases the activity of maltolytic ferment. It acts irregularly on glycolytic ferment and has no influence on the ferments which act on dextrin and glycogen. Incidentally, Hugounenq and Enselme noted a ferment in the blood which hydrolyzes insulin. These studies show that although insulin does influence carbohydrate metabolism, its action is very complex and its mechanism is still difficult to follow.—R. G. H.

The action of pepsin on insulin. Epstein (A. A.), Proc Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 9-11.

A mixture of insulin and pepsin was acidified. This when tested by injection into animals showed no insulin activity. Activity can be restored by proper neutralization even though the mixture has stood for 4 days at body temperature. Pepsin, therefore, does not digest insulin but inactivates it in some other way.—J. C. D.

The relation between the pancreas and the carbohydrate metabolism of muscle. I. The effect of extracts from the gland on lactic acid production in vitro. Foster (D. L.) & Woodrow (C. E.), Biochem. J. (Liverp.), 1924, **18**, 562-575.

The presence in the pancreas of a factor which is capable of causing a marked inhibition in lactic acid production of chopped muscle is shown. This inhibitory factor is neither trypsin nor insulin and probably not antiglyoxalase. A method is described for making a stable preparation of the pancreas with all its enzymes intact, and details are given for making an extract of this preparation with 70% alcohol which contains the inhibitory factor in high concentration.—F. S. H.

The blood sugar reducing properties on plant extracts and oxydases together with the proof of enzymes in insulin (Ueber die blutzuckerherabsetsetzende Wirkung vom Pflanzenextrakten und Oxydasen sowie den Nachweis von Fermenten im Insulin). Glaser (E.) & Wittner (L.), Biochem. Ztschr. (Berl.), 1924, **151**, 279-305.

Substances which cause a lowering of blood sugar in rabbits

were extracted from fungi (mushrooms) and turnips. The extract of the former obtained by the use of acid-alcohol was inactive. It is possible that a part of this activity is attributable to oxydase enzymes present in the original material. Such oxidizing enzymes were demonstrated in insulin. Peroxydase and aldehydase in particular were shown. These same enzymes were found also in the liver, pancreas and muscles.—F. S. H.

The influence of insulin on the respiratory metabolism of normal rabbits. Hawley (Estelle E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 66-67.

The author concludes that insulin, when administered to normal animals, brings about first a slight decrease, then a decided increase in the R. Q. curve, reaching the peak 2 hours after injection and returning to the basal level 4 hours later. A blood sugar drop accompanies the R. Q. change, the lowest blood sugar occurring at the peak of the curve. The return to normal is less rapid than the return to normal of the R. Q., though the curve is well on its return by the end of the 4 hours. There is, in the second hour, both a decrease in the O_2 and an increase in the CO_2, both changes tending to increase the R. Q. The O_2 consumption and the heat production would indicate that the total metabolism is not markedly increased.
—J. C. D.

Diabetes in an infant treated with insulin with severe cutaneous reactions (Un cas de diabète infantile traité par l'insuline avec accidents cutanés graves: l'erythrodermia édémateuse insulinienne). Lereboullet (P.), Lelong (M.) & Frossard (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 1189-1190.

The infant received early in the insulin treatment for its diabetes preventative inoculations for rugeola and diphtheria. About a week later urticarial lesions appeared half an hour after the injections of insulin. Five days later this became complicated by a generalized edematous condition. Withholding of insulin was followed by recession of the urticaria and edema. Renewal of insulin administration resulted in reappearance of the cutaneous disorders. Later rugeola came on and was recovered from, but the cutaneous reactions to insulin continued up to the time of death.—F. S. H.

Vomiting of pregnancy with acidosis treated by insulin (Un cas de vomissements gravidiques à caractére incoercible avec état d'acidose très prononcé et traité par l'insuline). Lequeux, Weill (A.) & Laudat, Gynéc. (Par.), 1924, **23**, 408-409. See also: Bull. d'obst. et de Gynèc. (Par.), 1924, **13**, 348-355.

Favorable results are reported using 10 units of insulin. Recurrences occurred, but they were amenable to additional insulin administration.—F. S. H.

The pharmacological assay of insulin. MacLeod (J. J. R.), & Orr (M. D.), J. of Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 137-138.

Rabbits starved for 24 hours were used. Originally one unit of insulin was defined as that amount which would lower the blood sugar of a normal rabbit to the convulsive level (0.045%) in 5 hours (physiological unit). This unit has been changed to one-third of the original unit (clinical unit). To make the definition inclusive and to allow for the duration of the hypoglycemia as well as the varying weight of the animals, the following equation is used:

$$\text{units per cubic centimeter equals} \quad \frac{a}{b} \times \frac{w}{c} \times 1.5$$

"a" is the difference between the normal blood sugar and the average of the blood sugars at 1½, 3 and 5 hours after injection; "b" is the difference between the normal blood sugar and 0.045; "c" is the number of cubic centimeters of insulin injected, and "w" is the weight of the rabbit in kilograms. The factor 1.5 is used because the original unit was based on the effect produced in the rabbit weighing 2 kgm., and the clinical unit is one-third the physiological. The method of carrying out the assay is given.—G. E. B.

The significance of glycosuria. Marsh (P. L.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 663-674.

Glycosuria should lead to the suspicion of diabetes mellitus until proved otherwise. It must be remembered that there are other syndromes of which glycosuria is a constituent. Whatever the mode of treatment adopted in a case of diabetes, it is of primary importance that the diabetic be kept in a sugar-free state.—I. B.

The perlingual administration of insulin (Uber die perlinguale Applikation des Insulins). Mendel (B.), Wittgenstein (A.) & Wolffenstein (E.), Klin. Wchnschr. (Berl.), 1924, **3**, 470-472.

When a solution of insulin is placed in the mouth, the active constituent is absorbed and exerts its customary action on carbohydrate metabolism. The practical significance of this discovery is far reaching because if this mode of application should prove to be universally successful, the disagreeable hypodermic administration could be done away with.—Chem. Abst., **18**, 3219.

Behavior of the blood sugar in the rabbit under various conditions and its distribution in the blood (Ueber das Verhalten des Blutzuckers beim Kaninchen unter verschiedenen Bedingungen und über seine Verteilung im Blut). Mochizuki (N.), Biochem. Ztschr. (Berl.), 1924, **150**, 123-143.

When the pancreatic duct is tied off in rabbits the blood sugar rises and then falls after a few days. It rises again and tends to maintain this condition. The first rise has its origin in a flooding of the blood and tissues with diastase and the glycogen breakdown therewith connected; the second is attributable to the gradually developing sympathicotonic condition. The same behavior is exhibited in experimental animals after glucose administration. **Adrenalin** injection into the experimental animal produces a like reaction, e. g., increased rise in blood sugar and a delayed fall. In the normal animal 25% of the blood sugar is found in the corpuscles and 75% in the plasma. In the experimental animal the corpuscular sugar content rises to 43% and then falls to the original value, without rising again. The increase in blood sugar which takes place in the normal animal after pilocarpin injection is inhibited in the operated rabbit. Phloridzin administration is followed by a fall in blood sugar in the animal with the pancreatic duct tied off.—F. S. H.

Insulin and the skin. Müller (E. F.) & Corbitt (H. B.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 608-617.

Experimenting on rabbits, the authors found that there is a decided difference between the results of subcutaneous and intradermal injections of insulin. The effect of insulin is considerably prolonged if given by the intradermal route. Fatal doses with the intradermal route may be higher than fatal doses by the subcutaneous.—I. B.

The normal value of the threshold for sugar excretion (Ueber den normalen Wert der Zuckeraussheidungsschwelle). Nakayama (M.), J. Biochem. (Japan), 1924, **3**, 407-422.

The threshold for sugar excretion in non-diabetic, healthy and diseased persons ranged from 0.08 to 0.21%, with the maximum number of cases falling between 0.13 and 0.19%. Values below 0.12 and above 0.20 were rarely encountered. No marked differences were found between the **diabetics** and the non-diabetics, though it must not be overlooked that higher values were the rule in the former and lower in the latter. Sex seems to have no influence on the value; but age does in the sense that there is a tendency for the values to increase with age.—F. S. H.

Experiences with insulin treatment in childhood (Erfahrungen über Insulinbehandlung im Kindesalter). Priesel (R.) & Wagner (R.), Ztschr. f. Kinderh. (Berl.), 1924, **38**, 103-117.

Severely afflicted **diabetics** must undergo protein restriction even with insulin. Blood sugar determinations are necessary in childhood. In diabetic coma large doses of insulin and glucose and liquids are indicated. The danger of overdosage with insulin is greater in childhood than in adulthood. The carbohydrate toler-

ance of the person may be raised by insulin treatment if the disease has not progressed too far. The intoxication following overdosage with insulin is quite similar to the picture produced in Rowntree's "water intoxication."—Am. J. Dis. Child., **28**, 633.

Diabetic coma with pulmonary tuberculosis treated with insulin (Coma diabetique et tuberculose pulmonaire. Traitement par l'insuline). Rathery (F.) & Dreyfus-Sée., Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 973-979.

A case report in which the following points are emphasized: 1. rarity of coma in a tubercular diabetic; 2. complete cure of the coma by insulin for 3 months; 3. The lack of association between excretion of acetone bodies and beta-oxybutyric acid; 4 the need for large doses of insulin.—F. S. H.

The production of lactic acid in diabetes following the administration of insulin. Tolstoi (E.), Loebel (R. O.), Levine (S. V.) & Richardson (H. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 447-452.

Four patients with uncomplicated diabetes were studied. The results were contrasted with those obtained with 4 non-diabetics who were injected with adrenalin. It was concluded that both extracts lower the inorganic phosphate of the blood. Extreme drops in blood sugar may occur with no change in the lactic acid concentration. Increases in lactic acid were observed only when insulin hypoglycemia was produced. Lactic acid increases with adrenalin hyperglycemia. Insulin causes an increase in the respiratory quotient beyond what can be accounted for by the production of lactic acid. This is evidence of the stimulating action exerted by the extract on the oxidation of carbohydrate.—J. C. D.

The effect of insulin upon the rate of fermentation of glucose by yeast. Travell (J. G.) & Behre (J. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 478-479.

Insulin fails to influence the rate of fermentation. The action of insulin in the body is, therefore, probably not upon the glucose molecule itself.—J. C. D.

Does the pancreatic hormone (insulin) lower the blood pressure? Weinberger (W.) & Holzman (A.), J. Am. M. Ass. (Chicago), 1924, **83**, 1215-1216.

In the course of treatment of patients with diabetes mellitus, Weinberger and Holzman made the following observations: 1. Under insulin administration, a number of diabetic patients with hypertension showed a diminution in blood pressure. 2. Some with a normal or low blood pressure exhibited a still further lowering. 3. The factor of blood sugar reduction is independent from the factor of blood pressure reduction, since many lowered blood pres-

sure readings were obtained though the blood remained hyperglycemic on account of the diet being adjusted to that effect. Four cases are here cited. The capacity of insulin to reduce the blood pressure under certain conditions was also observed by Klemperer and Strisower, who obtained similar, though not identical, experimental results. The authors raise the question: Does not insulin, representing, as it does, the internal secretion of the pancreas (if there should be an etiologic relationship between it and the lower blood pressure observed), act in conformity with the hypothesis of an antagonistic action between the hormones of the pancreas and suprarenal glands? That the height of the blood pressure bears some relationship to the concentration in the circulating blood of the suprarenal hormones is now generally recognized. Therefore, the administration of insulin should have a tendency to lower the blood pressure, which should occur the more easily in conditions with hypofunction of the suprarenal glands, so that a syndrome analogous to Addison's may result.—Courtesy A. M. A.

A crystalline substance from the parathyroid glands that influences the calcium content of the blood. Berman (L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 465.

The substance, extracted from ox parathyroids with acidified alcohol, produced a definite increase in the calcium content of the blood when injected into the circulation. No report on methods or experimental evidence is given.—J. C. D.

On the efficacy of various calcium salts in parathyroid tetany. Compere (E. L.) & Luckhardt (A. B.), Proc. Soc. Exper. Biol. & Med (N. Y.), 1924, **21**, 526-528.

Calcium carbonate, nitrate or acetate may be substituted for calcium lactate to prevent tetany in dogs. The carbonate is more constipating than the lactate, while the other two are irritating to the gut. Soluble calcium phosphate is irritating, produces untoward symptoms and seems even to increase the tetany.—J. C. D.

The present position of parathyroid therapy. Critchley (M.), Practitioner (Lond.), 1924, **113**, 56-62.

The author reviews briefly our knowledge of the parathyroid and takes up the conditions in which parathyroid treatment might reasonably be supposed to be of value. He found in personal practice that it was useful in treating paralysis agitans, particularly the senile type, in varicose ulceration of the leg and in Graves' disease. It had a slight influence in reducing the intensity of the paroxysms in whooping cough. Warning is given of the danger of overdosage.—J. C. D.

Experimental tetany and diet. Inouye (T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 49-51.

In dogs following thyroparathyroidectomy, lactose in large quantities helped protect the animal from tetany. Tetany was invariably associated with low blood calcium and there was a parallelism between the lowering of the calcium and the severity of the symptoms. The author regards this change in calcium as secondary to "a complicated disturbance of metabolism in which protein metabolism plays some role."—J. C. D.

Increased gastrointestinal permeability as a possible factor in parathyroid tetany. Luckhardt (A. B.) & Compere (E. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 523-526.

Increased permeability of the gut to the toxic products producing tetany might explain the attacks following parathyroid removal. Dogs, which have recovered from the acute effects of parathyroidectomy, can be thrown into tetanic convulsions by doses of croton oil or cascara or sulphur ointment. This indicates that increased permeability of the gut from whatever cause is a factor in producing convulsions. The authors point out the danger in the light of these results of giving violent cathartics in epilepsy.

—J. C. D.

Autoplastic and homoplastic parathyroid transplantation. Swingle (W. W.) & Nicholas (J. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 429-433.

Tables showing experimental results on 34 cats are given. Homoplastic grafts were unsuccessful, while the autoplastic persisted and seemed to give some protection against tetany.—J. C. D.

Recent investigations on tetania parathyreopriva and idiopathic tetany and on the functions of the parathyroids. Paton (N.), Edinb. M. J., 1924, **31**, 541-559.

The author discusses 59 papers published since 1916. He concludes that the increased muscular tone which generally follows removal of the parathyroids indicates that these structures exercise an influence upon the tonus of skeletal muscles. The marked increase of muscle tone and the close similarity of the other symptoms to those produced by removal of the parathyroids which follow the administration of guanidin and its methyl compounds seem to show that they play a part in the maintenance of that tone. The fact that these substances are increased in the blood and urine after parathyroidectomy, and in the urine in idiopathic tetany, suggests that their metabolism is controlled by the parathyroids and that it is through them that muscular tone is regulated. The immediate action of these substances in one adequate dose is undoubtedly to

stimulate the efferent neurons of the spinal cord, and in a moderate dose to increase the excitability of the neuro-myons. But with repeated doses they apparently become anchored upon these structures to produce a condition of facilitated activity, and this is probably their chief mode of action in tetany. That a decrease in the calcium of the blood is not the primary factor in the causation of the symptom is shown by the effect of bleeding and transfusing a calcium-free solution, and further by the fact that a decrease in the calcium of the blood may occur without tetany, e. g., in uremia, and that tetany may occur without a marked fall in the calcium. There is no conclusive evidence to show whether this fall, when it occurs, is a result of the increase in the methyl-guanidin or a concomitant of it. No satisfactory explanation of the rise in the phosphates has been given, although the results of Greenwald and György indicate that there may be a decreased excretion. There is no indication that the increase in the phosphates plays a direct part in the production of symptoms. Accepting the evidence that the parathyroids influence the tone of muscles, they seem to do so by controlling the metabolism—production or destruction, or both—of the methyl-guanidins. Evidence has been adduced that methyl-guanidins and creatin may be derived from the cholin of the lecithin molecule. There is some indication that an excess of guanidins may be detoxicated by conversion to creatin. There seems to be no doubt that the precursors of the methyl-guanidins are endogenous, although possibly the products of the digestion of meat, etc., may also furnish precursors.—J. C. D.

Regeneration of the thymus following double suprarenalectomy in the rat. Jaffe (H. L.), J. Exper. M. (Balt.), 1924, **40**, 325-342.

In this paper is presented evidence that close interrelationship exists between the thymus and suprarenal glands in the rat. The data consists of protocols from 66 double suprarenalectomized rats of varying ages and 21 controls. It was found with great consistency that the removal of the suprarenals resulted in hyperplasia of the thymus in adult rats. The enlargement which was at its maximum after 3 to 5 weeks was more pronounced in the female than in the male. This effect on the thymus is believed to result from a disturbance of the interrelations between the gonads, the thymus and the interrenal glands. A possible relationship between the thymic enlargement of **Addison's disease, exophthalmic goiter** and status lymphaticus and that following double suprarenalectomy is suggested.—I. M.

Direct evidence of regeneration of the involuted thymus following double suprarenalectomy in the rat. Jaffe (H. L.), J. Exper. M. (Balt.), 1924, **40**, 619-625.

A portion of the thymus was removed in each of 13 old rats

for a control and 13 to 17 days later bilateral suprarenalectomy was performed. The histological appearance of the remaining thymus tissue several weeks after suprarenalectomy was then compared with that of the thymus before this operation. In control animals in which the effect of partial thymectomy alone was studied, no regeneration was observed. However, regeneration after suprarenalectomy was found to occur with striking constancy. The maximum degree of regeneration appeared within two weeks after the suprarenalectomy.—I. M.

Influence of thymus upon skeletal growth as shown by tissue culture and extirpation methods (Uber den Einfluss des Thymus resp. dessen Extraktes auf das Knochenwachstum studiert sowohl durch Gewebskultur als auch durch Extirpationsversuch). Katsura (H.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, **30**, 177-206.

Removal of the thymus is comparatively easy in birds because the gland lies quite outside the thorax. Extirpation of the thymus in young birds is followed by a rapid differentiation and early attainment of adult characters. Birds from which the gland has been removed show a lower calcium content in bones and the females lay eggs with less calcium than normal in the shells. When added to tissue cultures, in which it is unaided or unopposed by other incretory glands, the thymus accelerates growth.—W. J. A.

The influence of thyroidectomy, gonadectomy, suprarenalectomy and splenectomy on the thymus gland of rabbits. Marine (D.), Manley (O. F.) & Bauman (E. J.), J. Exper. M. (Balt.), 1924, **40**, 429-443.

The data were obtained in a comprehensive study of the effects on the remaining tissues of the body after the various operations mentioned in the title. The results presented were taken from 373 completed protocols in which the thymus and the lymphoid tissues were studied. Thyroidectomy hastens while gonadectomy delays involution of the thymus. Suprarenalectomy not only delays involution but even causes regeneration of both thymus and lymphoid tissue. Thyroidectomy prevents this reaction even with combined suprarenalectomy and gonadectomy. Combined suprarenalectomy and gonadectomy is more effective than either alone and causes a true lymphoid and thymus hyperplasia. This causes a syndrome resembling status lymphaticus and is thought to be independent of any chromaffin tissue deficiency. Thymus and lymphoid hyperplasia in infancy are believed to be manifestations of interrenal and gonad functional underdevelopment. The so-called lymphatic constitution which underlies or accompanies exophthalmic goiter, **Addison's disease** and **acromegaly** is thought by the authors to be dependent upon a partial suppression of certain functions of the interrenal and sex glands.—I. M.

The thymic constitution. Schridde (H.), München. med. Wchnschr., 1924, **71**, 1533-1534.

Schridde has encountered since 1914 five new cases of hyperplasia of the medulla of the thymus in new-born boys. The infants were fat and excessively large (one of them measured 61 cm.). He emphasizes the significance of the hyperplasia of the thymus medulla. The combination of the swelling of the follicles of the spleen and the intestines, the abnormal height, and the abundance of fat occurs only with this form of thymus hyperplasia.

—J. Am. M. Ass., **83**, 1961.

The thymus gland in the Chinese. Shellshear (J. L.), China M. J. (Shanghai), 1924, **38**, 646-657.

The cervical portion of the thymus gland of the Chinese is well marked, and is represented by two distinct lobulated extremities which reach, and in some cases pass under, the **thyroid** gland. Microscopic examination shows that regressive changes are later here than elsewhere, and the gland is therefore cervico-thoracic in the Chinese, whereas in the adult European it is mostly a thoracic structure. Of 100 subjects, examined post-mortem, varying from 12 to 87 years of age, 11 had glands that were abnormally large (group 1), including 2 over 30 years of age. Group 2 contained 40 subjects, and the glands of these weighed from 35 to 40 grams; group 3 (medium size) contained 23; group 4 (gland small) contained 14; and group 5 (gland insignificant) had 8. The thymus was absent in 4. It is thus evident that the gland is both larger and more persistent than in the European. Microscopic examination showed the large size to be due to thymic tissue. An abundance of parenchyma is held until a later age than in the European. A rather far-fetched theory of sexual selection of a thymic type is offered as an explanation of the facts observed. A more plausible suggestion is also made that the persistent thymus might be acquired in the Chinese, due to frequent exposure to infection.

—L. G. K.

Endocrine origin of thymic asthma. Werneck (C.), Deutsche Ztschr. f. Chir. (Leipz.), 1924, **187**, 133-138.

A male infant, aged 3 months, had had stridor from birth, and was unable to nurse properly on account of disturbance in respiration. The clinical picture was that of thymic asthma, with spasms of cyanosis and intense dyspnea lasting for 2 hours and followed by a profuse flow of mucus. The thymus did not seem to be enlarged, and there was nothing to indicate disease of the bronchial or tracheal glands. The stridor accompanied both inspiration and expiration; the lower ribs were drawn in as inspiration began and then were protruded. Werneck proposed thymectomy but the family declined. The child was brought in asphyxiated a few days later,

in deep cyanosis and apparently dead. Without any attempt at anesthesia the right lobe of the thymus was removed. It weighed 5 gm. and was macroscopically normal, but the microscope revealed histologic changes. The total weight of the thymus can be estimated at 9 gm., which is within normal range, and there could not have been compression of the air passages or nerves. All the symptoms gradually disappeared, the stridor the second day. There has been no tendency to suffocation or cyanosis since the fourth day, and the child in 2 months had gained 1,200 gm. These facts can be explained only by assumption of excessive endocrine functioning of the thymus as responsible for the respiratory disturbances, cured by partial thymectomy.—J. Am. M. Ass., **83**, 1380.

The thyroid and specific dynamic action. Preliminary report. Baumann (E. J.) & Hunt (L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 447-448.

Six rabbits were used. The increased heat production found normally following the ingestion of glucose does not take place in the absence of thyroid tissue. Some specific dynamic action results, however, if even a small amount of thyroid (1/20 of the normal) is present and physiologically active.—J. C. D.

Prophylaxis and treatment of goiter by iodine (Profilaxia y tratamiento del bocio por el iodo). Bonilla, Med. ibera (Madrid), 1923, No. 317, 456-459.

The theory which seeks to explain the cause of goiter as due to absence of iodine in the food is today conceded to be of great importance. Although it has not been completely proved which of the many current theories is correct, it is undoubtedly true that iodine plays a very important part in the normal physiology and pathology of the thyroid, and this fact forms the basis of the modern prophylaxis and treatment of goiter. Good results are obtained from the use of iodine in sporadic goiter of the adult, being principally advocated in diffuse goiter, although it is possible to secure good results in cases accompanied by small nodular formations. Small doses should be used—3 mg. daily for 75 days, or once or twice per week for several months. There is danger in this medication of causing Basedow's disease, although this is very rare with the doses and care employed at present. Basedow's disease is more or less easily produced according to the region. In Spain it is quite frequent, especially in the goitrous regions. In spite of the fact that some advise iodine therapy even in Basedow's disease, Bonilla agrees with the majority of investigators that iodine is contraindicated when there exist the slightest symptoms of hyperthyroidism and that it ought to be employed in the prophylaxis and treatment of goiter only in very small doses.—G. M.

Certain pathological tissue changes in thyroidectomized sheep. Goldberg (S. A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 567-568.

Several thyroidectomized lambs showed subcutaneous and subserous edema, ascites, hydrothorax, parenchymatous nephritis and aortic changes. The last occurred both in the systemic and pulmonary aortas and consisted of degeneration and calcification of the media in the form of placques. Some or all of these changes appeared in 5 of 10 animals from 8 months to 2½ years after operation. Twin controls were healthy.—J. C. D.

Production of goiter in rats by restricted iodine feeding. Hayden (E. M.), Wenner (W. T.) & Rucker (C. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 546-547.

Rats fed an iodine-poor diet showed thyroids averaging twice the size of those in the controls whose drinking water contained 0.1 mg. of iodine per liter. Six experimental and six control animals were used.—J. C. D.

The action of thyroid and iodine preparations fed to frog larvae. (Zur Fütterungswirkung von Schilddrüse und Jodpräparaten auf Froschlarven). Kahn (R. H.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 404-414.

Various effects were produced by feeding different thyroid preparations, thyroid derivatives, and iodine preparations—from rapidly developing malformations and death on the one hand to mild effects resulting after a longer time through accelerated metamorphosis in non-malformed dwarfs, depending essentially on the differing amounts of iodine administered. Thyroids from subjects of **Graves' disease** produce much less effect than normal glands. Venous blood from dog thyroids produces no demonstrable effect. **Antithyreoidin** (Moebius) does not inhibit the effect of small doses of thyroid. Feeding the body substance of frog larvae at the height of the thyroid effect on them has no effect on other larvae so fed. Thyroid effect varies with the diet fed, as stated by Jarisch, but only under special experimental conditions. Of various commercial artificially iodized products tested only iodalbacid and iodglidin were effective. Iodine tincture fed with meal has a marked influence on growth and metamorphosis. Hence it would appear that the effectiveness of thyroid and of iodine compounds depends on special types of iodine linkage in the molecule, and not on iodine action per se.—A. T. C.